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SACCHARIN: TECHNICAL ASSESSMENT OF RISKS AND BENEFITS

Report No. 1

Committee for a Study on Saccharin and Food Safety Policy

Assembly of Life Sciences/Institute of Medicine
National Research Council/National Academy of Sciences
Washington, D.C., November 1978

NOTICE

The project that is the subject of this report was approved by the Governing Board of the National Research Council, whose members are drawn from the Councils of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine. The members of the committee responsible for the report were chosen for their special competences and with regard for appropriate balance.

This report has been reviewed by a group other than the authors according to procedures approved by a Report Review Committee consisting of members of the National Academy of Sciences, the National Academy of Engineering, and the Institute of Medicine.

The work on which this report is based was performed pursuant to Contract No. 223-78-2145 with the Food and Drug Administration.

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COMMITTEE CHAIRMAN'S PREFACE

The issues surrounding the use of food additives have generated considerable controversy during the past few years. In Congress, the debate reached its peak in regard to the possible ban on the use of saccharin. In November 1977 this culminated in the passage of the Saccharin Study and Labeling Act (PL 95-203). The Act requested that the National Academy of Sciences examine the risks and benefits to health of the use of saccharin and consider the more general issues surrounding federal food safety policy.

A coordinating committee and two panels--one to address the saccharin issue and one to examine the general food safety policy--were established by the National Academy of Sciences for this study. The panels and the coordinating committee, which shares responsibility for the content of the report, included biomedical scientists and clinicians with a variety of expertise, lawyers, economists, political scientists, and persons representing the broad public interest. (Membership of these groups is listed in the front of this report.)

Because of the diverse backgrounds and points of view represented, as well as the complexity of the subject, effective communication and consensus building were not easy. Nevertheless, as the chairman of the coordinating committee, I was most gratified to observe the rapidity with which the group developed cohesiveness and members displayed respect for each other's views.

Panel I, whose work focused on saccharin, was organized within the Assembly of Life Sciences. Its report was due November 1, 1978. The panel's illustrative case study of saccharin is presented as Part I of the committee's final report.

The basic charge contained in the Act regarding saccharin was that a study be conducted

> "to determine, to the extent feasible--
> (A) the chemical identity of any impurities contained in commercially used saccharin, (B) the toxicity or potential toxicity of any such impurities, including their carcinogenicity or potential carcinogenicity in humans, and (C) the health benefits, if any, to humans resulting from the use of nonnutritive sweeteners in general and saccharin in particular."

The saccharin report presents some conclusions, with varying degrees of certainty. But because of the shortage of time, Panel I makes no specific recommendations regarding the use of saccharin. The results of Panel I's discussion about the possible policy in this area will be presented in Part II of the report, in the context of broader food safety policy.

Panel II, which considered general food safety policy issues, was organized within the Institute of Medicine. Its report--Part II of the committee's final report--is due February 1, 1979, and will respond to the charge of the Act that requested

> "a study, based on available information, of (A) current technical capabilities to predict the direct or secondary carcinogenicity or other toxicity in humans of substances which are added to, become a part of, or naturally occur in, food and which have been found to cause cancer in animals; (B) the direct and indirect health benefits and risks to individuals from food which contain carcinogenic or other toxic substances; (C) the existing means of evaluating the risks to health from the carcinogenicity or other toxicity of such substances, the existing means of evaluating the health benefits of foods containing such substances, and the existing statutory authority for, and appropriateness of weighing such risks against such benefits; (D) instances in which requirements to restrict or prohibit the use of such substances do not accord with the relationship between such risks and benefits; and (E) the relationship between existing Federal food regulatory policy and existing Federal regulatory policy applicable to carcinogenic and other toxic substances used as other than foods."

In examining the broad issue of food safety, the panel gave major attention to the problems of food additives and contaminants, less consideration to potentially harmful natural substances, and little or no consideration to the effect of dietary patterns on health. The technical means of evaluating risks and benefits were studied, and an effort was made to delineate clearly their potential usefulness and limitations as a basis for formulating food safety policy.

Ideally, food safety regulation would be simple, efficient, responsive, scientifically based, and would allow for minimal interference with personal freedom and maximal public participation, while providing the greatest possible protection for consumers. These elements were used as reference points in the study, although a perfect system is probably unattainable.

The committee, panel, and staff found the subject of food safety policy to be too complex to deal with comprehensively in the 18 months allotted for this study and therefore limited the analyses presented in this report to those issues that could be covered reasonably well. This report supplies some of the data, information, and ideas that are needed for reevaluating national food safety policy, but it should be considered only a first step in this difficult task. Clearly, food safety policy deserves a thorough, thoughtful analysis and periodic review, as it is a vital part of federal efforts towards enhancement of the public's health.

Frederick C. Robbins
Chairman
Coordinating Committee for a Study
on Saccharin and Food Safety Policy

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PANEL CHAIRMAN'S PREFACE

The Panel on Saccharin and its Impurities, interacting with the Committee on Saccharin and Food Safety Policy, addressed a charge that included specific requests in Public Law 95-203 to examine the chemical identity and potential toxicity including carcinogenicity of impurities in commercially used saccharin and a study of the possible health benefits of nonnutritive sweeteners in general and saccharin in particular. These topics have been addressed in Chapters 3 (impurities) and 4 (benefits). However, the evaluation of saccharin impurities cannot be separated entirely from the evaluation of saccharin itself. Therefore, all the available data on saccharin of varying degrees of purity, including some new data not included in previous evaluations, have been reviewed.

The panel met many times--as a whole, as subpanels, or together with committee members--to discuss and arrive at the conclusions that are detailed in this report. As Chairman, I thank the members for their dedicated efforts in completing the report under severe time constraints.

The panel was helped immeasurably by the willingness of individuals, professional groups, government agencies, and trade organizations to share their information and insights. In addition, it received information on June 19, 1978, at a public meeting that provided an opportunity for any person to place information before the panel. Consultants to Panel I included Israel J. Abrams, Market Research Corporation of America; Sidney Abrams, National Center for Health Statistics, U. S. Department of Health, Education, and Welfare; Bruce Armstrong, Public Health Department,

Australia; Douglas L. Arnold, Canadian Health Protection Branch; Louise Ball, University of Southhampton, England; Howard Bauman, Pillsbury Company; J. S. Bennett, Canadian Medical Association; David Burch, Canadian National Cancer Institute; Thomas Coates, Stanford University; Ell Dee Compton, Sherwin-Williams Company; Thomas Dailey, National Soft Drink Association; Phil Derse, Raltech Scientific Services, Inc.; Kenneth Doyle, National Soft Drink Association; Arnold Engel, National Center for Health Statistics, U. S. Department of Health, Education, and Welfare; Robert Gelardi, Calorie Control Council; Jan Goeller, Canadian Diabetics Association; Kenneth Gorman, Canadian Diabetics Association; Frederick Gray, U.S. Department of Agriculture; Thomas Greer, U.S. International Trade Commission; William Hale, Arthur D. Little Inc.; Marian Hicks, Middlesex Hospital Medical School, England; Jules Hirsch, Rockefeller University; Robert Hoover, National Cancer Institute; Norman Holly, U.S. Agency for International Development; Jeffery Howe, Canadian National Cancer Institute; Nobuyuki Ito, Nagoya University, Japan; Irving I. Kessler, University of Maryland School of Medicine; Larry Larkin, U.S. Department of Agriculture; Thomas Linscheid, Georgetown University; James Lowe, Canadian Diabetics Association; Anthony J. McMichael, Commonwealth Scientific and Industrial Research Organization, Australia; Ferd Meyer, Monsanto Chemical Company; A. J. Miller, Canadian National Cancer Institute; A. Moodie, Canadian Health Protection Branch; Allan Morrison, Harvard School of Public Health; Ian Munro, Canadian Health Protection Branch; Eleanor Pao, U.S. Department of Agriculture; Henry Pitot, McArdle Laboratory for Cancer Research, University of Wisconsin; Richard Salkeld, F. Hoffmann-La Roche, Inc., Switzerland; Albert Segaloff, Alton Ochsner Medical Foundation; Eugene Soares, Chemical Industry Institute of Toxicology; Robert Squire, Johns Hopkins University; Bozidar

Stavric, Canadian Health Protection Branch; Steven Stellman, American Health Foundation; Trisha Strasser, National Cancer Institute; and Ernst Wynder, American Health Foundation. Among the many individuals at the Food and Drug Administration who provided background and other information were Arletta Beloian, C. Darnell Jackson, Jean Taylor, and Morris A. Weinberger.

Special thanks are due to the staff of the Assembly of Life Sciences without whose assistance it would have been impossible to prepare this report in this depth of analysis and completeness.

The short deadlines could not have been met without the invaluable secretarial assistance and typing of the many drafts by Waldena Banks, Susan G. Barron, Eileen G. Brown, Paula Hatcher, Jacqueline K. Prince, Normandy M. Schoen, and Joyce A. Russell, and the preparation of the references by Joan Semasinghe.

Emmanuel Farber, M.D., Ph.D.
Chairman
Panel I, Study of Saccharin and
Its Impurities

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EXECUTIVE SUMMARY

Historical Perspective

For more than 70 years saccharin has been used as a substitute for sugar in the United States. For almost that same length of time its safety has been the subject of controversy. In 1912, the substance was in fact banned from foods, but during World War I, the reduced sugar supply prompted the lifting of the ban.

Over the last quarter century, a number of factors have combined to focus attention on the potential risks of saccharin use and the possibility that it might be removed from use as a food additive. In addition to factors that are directly related to saccharin use, there are others that affect the climate in which a decision will be made regarding saccharin availability. Changing habits of food consumption and changing patterns of lifestyle have led to increased dependence on processed and convenience foods containing additives. The presence of these additives has aroused concern. In general, the safety of consumer products, of the workplace, and of the environment has become a matter of great interest to the public. Concern for personal health and appearance has propelled segments of the population toward weight maintenance and weight reduction programs. Approximately one quarter of the U.S. population uses products containing nonnutritive sweeteners and has become accustomed to their availability. At the same time science has greatly improved its techniques for detecting and evaluating hazardous substances. The public, representing a wide spectrum of opinions, has become more vocal and sophisticated in expressing its beliefs and desires.

In April 1977 the Food and Drug Administration proposed a ban on the use of saccharin as a food additive on the basis of demonstrated carcinogenic activity in laboratory animals. Reacting to public concern about

the loss of access to products containing the only nonnutritive sweetener on the market, Congress passed The Saccharin Study and Labeling Act (PL 95-203), which President Carter signed on November 23, 1977. This Act calls upon the National Academy of Sciences to study specific questions that are relevant to a decision on saccharin safety and requests studies on matters relating to food safety policy in general.

Chapter 1 of this report develops in greater detail the historical perspective on saccharin.

Consumption Patterns

Chapter 2 presents data on consumption patterns of saccharin. The data became available quite late in the course of the committee's deliberations and have not been fully analyzed. However, it is possible to draw from the data some estimates of the extent to which segments of the population are exposed to saccharin. From these data the committee estimates that approximately 50 to 70 million Americans now consume products containing saccharin. This estimate includes approximately 80% of the approximately 5 million people with diabetes and about a third of children under 10 years of age. Furthermore, the committee estimates that the average daily consumption ranges from 25 mg to 155 mg of saccharin for nondiabetic users and 54 mg to 173 mg for diabetic users. For comparison, a 12-oz bottle of diet soft drink contains about 150 mg of saccharin.

The committee calls attention not only to the increase in recent years in the number of persons using products containing saccharin but especially to the increased incidence of use among children under 10 years of age and the increase in the amount that the users in this age group consume. When expressed as consumption of saccharin per kilogram of body weight, the under

10 group consumes the highest amount of saccharin of any age group, as it does of most ingredients. A large part of the increased consumption is accounted for by diet soft drinks.

The committee recommends further research on consumption patterns. Since the consideration of risks and benefits may be influenced by the consumption pattern data, the question of whether the increase in saccharin consumption adds to or replaces sugar or other calorie consumption should be explored.

Risks of Saccharin Use

In Chapter 3 the committee has evaluated the data from laboratory animal studies, from other laboratory tests, and from epidemiologic studies.

The committee accepts the validity of the animal tests on saccharin.

In rats saccharin is a carcinogen of low potency relative to other carcinogens. The animal studies that are analyzed in Chapter 3 show that saccharin can act as an initiator of cancer. However, it has relatively low potency (i.e., when compared to other known chemical carcinogens, a far greater dose of saccharin is required to produce a standardized cancer incidence) and it exerts this effect only in male animals. Saccharin is most effective as an initiator when the mother is exposed before pregnancy, the fetus is exposed throughout gestation, and the exposure continues throughout the life of the offspring.

In addition to acting by itself, saccharin promotes the cancer-causing effects of some other carcinogenic compounds in rats. As stated above, saccharin alone can act as a carcinogen. Furthermore, data show that saccharin acts as a promoter of carcinogenicity in rats (i.e., when administered to animals that had been exposed previously to low doses of some other bladder carcinogens, it increases the incidence of bladder cancer in both

sexes). The distinction between an "initiator" and a "promoter" of carcinogenesis is important for two reasons: (a) it aids in the understanding of the mode of development of cancer, including that induced by saccharin, and (b) although the direct carcinogenic potential of saccharin in humans may be weak, its possible action as a promoter of cancer may be more important. (In laboratory animals, cancer can be induced by exposure to an initiator followed by prolonged exposure to promoters.) Whether an initiator or promoter, saccharin must be viewed as a potential cause of cancer in humans. However, our present state of knowledge does not permit us to distinguish between initiators and promoters in a regulatory context.

There are no other clear-cut chronic toxic effects that are associated with exposure of animals to saccharin. However, some studies indicate that saccharin consumption is associated with adverse effects in the female reproductive system.

Saccharin alone, not the associated impurities, is most likely responsible for these adverse effects. Chapter 3 contains an analysis of whether impurities are responsible for the carcinogenic effects of saccharin. Within the bounds of scientific certainty, the committee concludes that the carcinogenic potential resides in saccharin itself and cannot be reasonably ascribed to one or a number of impurities. This conclusion is based on the facts that the most highly purified saccharin that has been tested still causes cancer in animals, that all saccharin, which is prepared commercially by two quite different processes and which contains a different array of impurities, is equally carcinogenic in animals, and that, when tested alone, orthotoluenesulfonamide (OTS--a major impurity in the saccharin that was used in two studies showing saccharin to be a bladder carcinogen) has not produced cancer.

As for any chemical substance, absolute purity is not attainable for saccharin. Therefore, there have been no tests on "absolutely pure" saccharin, and it is unlikely that such a substance can be obtained. The committee exercises its scientific judgment in saying that the impurities of saccharin are not the cause of cancer that results from ingestion of saccharin by animals, unless the residual impurities are immensely potent carcinogens. The likelihood that this is the case is small.

The committee accepts the logic that results obtained from valid animal tests can, in principle, be extrapolated to humans. However, requirements for high doses and long periods of exposure, as well as our current inability to make quantitative extrapolations from animals to humans makes it impossible to estimate with confidence the magnitude of risk to humans from the use of saccharin.

The committee concludes that further laboratory studies to establish the carcinogenicity of saccharin are not needed under existing law. However, research leading to a better understanding of methods for qualitative and quantitative extrapolation, in-utero exposure, and the mechanisms of cancer promotion would be highly desirable.

The results of some short-term *in-vitro* tests are in accord with the results of animal cancer tests. Saccharin has been studied extensively in microbial and cell culture tests that determine the ability of substances to produce mutations or other manifestations of genetic damage. (Many mutagens are also carcinogens.) These tests, called "in-vitro tests" or "short-term tests," have shown saccharin to be weakly positive in a few cases but negative in most. This might be expected for a very weak mutagen. Furthermore, the data on promoter activity of saccharin in one in-vitro study also are in accord with the data from studies on promoter effects in rats.

The epidemiologic studies that are detailed in Chapter 3 do not provide clear evidence to support or refute an association between past saccharin use and bladder cancer in males. All but two of the studies either suffered from methodologic difficulties or were too insensitive for reliable measurement of a potentially low-level effect of saccharin use. Of the two most extensive studies, one shows a statistically significant excess number of cases of bladder cancer; the other does not.

Concerning the estimation of risks, the committee notes that when effects are weak, they are difficult to distinguish either from random variation or from the stronger influence of other carcinogens. This is particularly evident with bladder cancer. This form of cancer is known to be associated with cigarette smoking and occupational exposure to certain chemicals, each of which appears to be far stronger than a possible effect of saccharin. One can never be completely sure that small but significant effects are not being obscured by such variation or that an apparent effect is in reality not just part of the random variation itself.

The results of animal studies indicate that saccharin poses a potential carcinogenic risk to humans. Based on the laboratory and human population studies taken together, it is the committee's judgment that saccharin would be expected to be of low potency. The committee notes that even low risks to a large number of exposed persons may lead to public health concerns.

Benefits of Saccharin

The analysis of the possible health benefits of saccharin use, which appears in Chapter 4, was specifically requested in the Saccharin Study and Labeling Act. This analysis was one of the more difficult tasks undertaken

by the committee since data on possible benefits were found to be sparse and often inadequate. However, since such an analysis was specifically requested, the committee has made an effort to respond to the charge.

The committee has found no studies that permit objective assessment of the asserted health benefits of saccharin use. Although a nonnutritive sweetener can be substituted for a nutritive sweetener to reduce caloric intake without loss of sweetness, data available to the committee do not permit the evaluation of the efficacy of saccharin in the control of diabetes or body weight. This area requires further research, through long-term, well-controlled clinical trials, to determine if saccharin use is helpful to diabetics and to overweight persons. Also, although it is generally agreed that fermentable sugars are an important causative factor in dental caries, it remains unclear whether the use of nonnutritive sweeteners, including saccharin, has a major effect in decreasing the incidence or severity of this form of dental disease.

Diabetes and weight control. Most diabetics and many persons attempting to maintain or reduce their weight perceive saccharin-containing foods and beverages as beneficial. The perception of efficacy is also evident from the fact that a significant proportion of a survey sample representing office-based private physicians believe that saccharin products are useful for their diabetic patients, for patients being treated for weight problems, and for patients with other conditions. No study that meets the current criteria for an adequate clinical trial has been conducted explicitly to examine the effectiveness of saccharin in the control of weight or blood sugar levels. The studies on the use of nonnutritive sweeteners to manage obesity and those pertaining to diabetes were considered by the committee to be inadequate to either prove or disprove the alleged benefits of saccharin use.

The committee recognizes a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. At this time, the committee is unable to draw conclusions about the implications of the perceived need or reliance. Regarding the psychological benefits of saccharin use, the committee can say only that for many humans the desire for sweet taste is a demonstrable biological phenomenon and that a large segment of the population perceives sweetness without calories (for control of weight and other conditions) as a benefit. The available data have not yet confirmed or denied the validity of these perceptions as factors that have an impact on health or disease.

Furthermore, the committee is unable to forecast with accuracy whether the unavailability of saccharin would increase sugar consumption or if such an increase would lead to detrimental physical health effects. Estimates of detrimental effects can be made, but their usefulness is questionnable because the estimates are based, of necessity, on undependable assumptions for such parameters as the number of persons who would revert to the use of sugar and the amount of sugar that those individuals would consume. Recent history shows that the 1969 removal of cyclamates from the market resulted in a slight decrease in consumption of nonnutritive sweeteners, but there was no change in the pattern of increasing consumption of nutritive sweeteners. It is not clear whether or not the same would occur today if saccharin were restricted. Any increase in sugar consumption would be small on the average because saccharin, although 300 times sweeter than sugar, represents only about 6% of the total sweetness in the American diet.

The committee accepts the premise that the use of nonnutritive sweeteners in drugs and dentifrices presents insignificant risks and involves possible benefits. Most toothpastes contain saccharin. Many drugs,

especially those for children, are compounded with saccharin to improve palatability, thereby encouraging proper use of the products. That benefits result from such use may be a reasonable assumption. Moreover, the amounts of saccharin that are contained in these products are so minute that they present only a slight risk. Chapter 4 contains a detailed discussion on the benefits of saccharin.

This report does not contain recommendations as to whether or not saccharin should be continued in use as a food additive. On occasion, the committee has discussed a variety of policy options concerning the use of saccharin. Such options range from no human exposure to restriction of exposure (to specified age group or product) or to the continued use at the present rate. On one hand, scientists can assess risk but cannot decide for society what risk it would be willing to take. On the other hand, measurement of benefits is more complex: certain benefits may be objectively and quantitatively demonstrated (e.g., disease control by use of antibiotics); other benefits may be very difficult to measure objectively (e.g., effects of saccharin use on control of weight); and still other benefits may be so subjective as to defy quantitation (e.g., satisfaction engendered by sweetness without calories). Thus, while scientists can often contribute to some aspects of risk-benefit analysis, the ultimate judgment must be made through the sociopolitical process, taking scientific facts into account but incorporating subjective considerations as well. Policy options for saccharin and other food chemicals will be dealt with in depth in the second report.

On the basis of its review of the scientific evidence, the committee suggests that the following observations be considered when arriving at policy decisions:

(1) In rats saccharin is a carcinogen of low potency relative to other carcinogens.

(2) In addition to acting by itself, saccharin promotes the cancer-causing effects of some other carcinogenic compounds in rats.

(3) Saccharin alone, not the associated impurities, is most likely responsible for these adverse effects.

(4) Whether an initiator or promoter, saccharin must be viewed as a potential carcinogen in humans, but one of low potency in comparison to other carcinogens. Although saccharin would be expected to be of low potency in humans, even low risks applied to a large number of exposed persons may lead to public health concerns.

(5) The state of the art in extrapolation does not permit confident estimation of the potency of saccharin as a cause of cancer in humans.

(6) Essentially, there is no scientific support for the health benefits of saccharin. Its potential benefits would include management of diabetes, obesity, hypertriglyceridemia, and tooth decay. The committee accepts the premise that the proper use of nonnutritive sweeteners in drugs and dentifrices presents slight risks and involves possible benefits.

(7) Although alleged psychological benefits of the use of saccharin and other nonnutritive sweeteners cannot be evaluated at this time, it is evident that segments of the population regard the substance as desirable.

(8) The observation that young children are becoming increasingly greater consumers of saccharin suggests that public health officials should take a prudent course of action since there has been insufficient time for the possible effects of this greater consumption to be manifest. This may be particularly important because of the anticipated long latent period between exposure to the potential carcinogen and the manifestation of cancer and because of the recently recognized promoter effects that have been exhibited by saccharin in laboratory tests.

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TECHNICAL SUMMARY

This section contains the summaries of Chapters 2 through 4.

CONSUMPTION OF SACCHARIN

The committee does not wish to draw definitive conclusions from the available data, but directs attention to the following apparent trends:

(1) The percentage of the population consuming saccharin-containing foods and the amounts consumed are both increasing. The percentage of young children that consume saccharin is also rising. Young children consume fewer total milligrams per user than do older persons, but the amount per unit of body weight often surpasses the intake among adults, the same as one would find with other food components. A major problem remains in interpreting these data: does the increase in saccharin consumption add to or replace sugar or other calorie consumption? The consideration of both risks and benefits will be influenced by the answer to this question. The committee recommends that further research be performed on consumption patterns.

(2) Whereas the percentage of women consuming saccharin was once considerably higher than the percentage of men, the margin of difference between the sexes has narrowed.

(3) Data indicate that the greatest users are now females in the child-bearing years (20- to 39-year age group) and males from birth to 9 years of age.

(4) Sixty to 90% of all diabetics (or those who classify themselves as diabetics) use saccharin extensively. A greater proportion of dieters (on low-calorie, low-cholesterol, low-fat, and other diets) consume saccharin than do nondieters.

(5) Soft drinks are the most frequently consumed saccharin-containing products on the market. They account for approximately 90% of the recent increased consumption of the sweetener.

RISK ASSESSMENT OF SACCHARIN AND ITS IMPURITIES

Laboratory Investigations

Based on the evaluation of the data from laboratory investigations of saccharin, the committee has reached the following conclusions about the toxicity and potential human risks from exposure to saccharin.

(1) Little biotransformation of saccharin has been detected in laboratory animals and none has been observed in humans. Because of the limits of experimental detection, it is possible that a small percentage of saccharin may be modified enzymatically. Saccharin is rapidly absorbed via the gastrointestinal tract, is distributed widely throughout the body, crosses the placental wall, and is eliminated mainly in the urine. Accumulations of saccharin in several tissues including the bladder have been demonstrated following repeated exposures.

The committee concludes that either saccharin is unusual in that its carcinogenic effects are due to the unmetabolized parent compound or the effects are due to small quantities of undetected metabolites. The accumulation of saccharin in the bladder epithelium may play a role in the formation of bladder cancer.

(2) When tested in two-generation studies, saccharin is a bladder carcinogen for male rats. A significant increase in bladder cancer was found consistently in male offspring exposed continuously in utero and throughout life. In one two-generation study, a significant increase in bladder cancer occurred in males of the parental generation.

Studies using saccharin in combination with some chemical carcinogens have shown that saccharin promotes tumor development in the bladder of rats. Since humans are exposed to a variety of chemical carcinogens in their environment, the carcinogenic risk from saccharin as a promoter may be considerably greater than that indicated by the single compound studies. Because the process of cancer promotion is little understood, the estimation of risks to humans from these experimental data are not feasible at present.

The committee concludes that the following factors in design of the two-generation chronic studies did not confound the interpretation of the results: the doses studied (maximum tolerated dose), in-utero exposure, high sodium content of diet in treated versus control animals, and the possibility of microcalculi in the urinary bladder of treated versus control animals.

Since animal studies that are properly conducted to detect carcinogenic activity are qualitatively predictive of human responses, the committee concludes that saccharin ingestion presents a predicted cancer risk to humans. However, because of the substantial uncertainties in extrapolating from experimental doses to human exposure levels, the committee concludes that quantitation of risks to humans cannot be made with confidence.

(3) An increase in benign uterine tumors and ovarian lesions in saccharin-treated rats was suggested in a few studies.

(4) Orthotoluenesulfonamide, the major impurity of saccharin manufactured by the Remsen-Fahlberg (RF) process, is not carcinogenic in rats in a study that is properly designed to detect carcinogenesis. The possibility that other minor impurities of saccharin are responsible for

carcinogenic activity of commercial saccharin cannot be eliminated. However, the committee believes that the probability of occurrence is extremely remote for the following reasons: (a) RF saccharin used in studies by the Food and Drug Administration and the Wisconsin Alumni Research Foundation had different patterns of impurities, yet produced the same carcinogenic responses (i.e., bladder cancer in males); (b) the very much purer Maumee process saccharin has also produced bladder cancer in males; (c) in Maumee saccharin the impurities are each present in such low concentrations that if they were carcinogenic, they would be required to be of exquisite potency.

(5) Short-term tests for genetic effects have been conducted with saccharin and some of its impurities. Results of 16 assays were negative, while those of five (including a promotion assay) were positive. Because these assays evaluate varying types of genetic effects and because saccharin appears to be a carcinogen of low potency, the variation in findings might be expected. The committee concludes that these studies are compatible with the in-vivo carcinogenic effects; however, the results do not provide definitive information on the interpretation of risks to humans.

Human Population Studies

The committee reviewed the epidemiologic studies of the relationship between saccharin and bladder cancer and between saccharin and spontaneous abortion. With one exception, findings indicated the absence of a health hazard for either sex. However, there were many deficiencies in the methods of the studies that showed no association.

(1) Time-trend studies by Armstrong and Doll in 1974 and by Burbank and Fraumeni in 1970 provide no evidence that saccharin use is necessarily associated with cancer. This method may be too insensitive to separate the effects of saccharin from known bladder cancer risk factors, such as

cigarette smoking, that have been changing over time.

(2) Studies on diabetics, by Armstrong et al. in 1976, by Armstrong and Doll in 1975, and by Kessler in 1970, do not show a positive association between saccharin use and bladder cancer, but these studies suffer from a number of limitations that hinder assessment of the risk of saccharin: (a) findings in diabetics may not be applicable to the nondiabetic population; (b) individual saccharin consumption was not measured; and (c) there were no data on smoking habits and certain occupations that are known to be associated with bladder cancer.

(3) The case-control studies do not provide clear evidence to support or refute an association between saccharin use and bladder cancer. Two studies of sufficient size for reliable measurement of low-level effects of saccharin use are those by Howe et al. in 1977 and by Kessler and Clark in 1978. The study by Howe et al. used a complex method to estimate the relative risk of bladder cancer in nonnutritive sweetener users and nonusers. This study reported that the proportion of male bladder cancer patients who used nonnutritive sweeteners is significantly higher (risk ratio of 1.6) than the proportion of male controls who used nonnutritive sweeteners. The study by Kessler and Clark reported no statistically significant excess risk for either sex, and is thus consistent with no excess cases of bladder cancer attributed to the use of saccharin. The committee believes that the methodologic difficulties of each study do not allow one to judge the seemingly contradictory results. Four other case-control studies--those by Kessler in 1976, Morgan and Jain in 1974, Wynder and Goldsmith in 1977, and Simon et al. in 1975--have failed to demonstrate a statistically significant risk, but these studies have major deficiencies which severely limit confidence in their findings.

The committee suggests two alternative sources that could be used to assess the risk of saccharin: data from prospective studies in which accurate dietary information had been collected and surveys to assess the risk of bladder cancer in workers who are involved in the production and handling of saccharin. These workers might be compared, both retrospectively and prospectively, with those employed in other areas of the same plant.

BENEFITS OF SACCHARIN

Data on the efficacy of saccharin in dietary management of health problems are sparse and, in many cases, inadequate. It is not possible either to rule out totally or to accept the claims of benefits made by some groups and there is no scientific evidence to show whether or not direct benefits to physical health from saccharin exist. However, no study that meets the current criteria for an adequate clinical trial has been conducted explicitly to examine the effectiveness of saccharin in the control of weight or diabetes.

It is not clear that the use of saccharin is associated with a diminution in the incidence of dental caries, for there have been no clinical trials on this subject. There are possible benefits in making dentifrices and therapeutic drugs more palatable in order to promote their proper use.

Human beings appear to have a marked predilection for sweet foods. The committee acknowledges a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. However, at this time the committee is unable to evaluate their significance or draw conclusions about their implications.

Concerning the benefits to physical health:

(1) Scientific evidence does not permit assessment of the role that saccharin plays in weight control or dietary compliance, both key factors in the prevention or treatment of obesity and diabetes. Five studies on management of obesity with nonnutritive sweeteners and three studies pertaining to diabetes were reviewed by the committee. It considered the design of the studies to be inappropriate for assessing the efficacy of saccharin in weight control or diabetic management.

(2) The information on the efficacy of saccharin in health maintenance, e.g., the dietary management of health problems, is sparse and in many cases inadequate.

(3) Long-term, well-controlled clinical trials using saccharin to control obesity or diabetes have not been performed. It is uncertain whether a satisfactory study can be designed to answer the necessary questions directly. The committee suggests that attempts at this type of study should continue and that short-term, retrospective, and other limited studies should be pursued to determine indirect estimates of benefits.

(4) The long-term consequences to diabetics of increased reliance on nutritive sweeteners have not been examined adequately.

(5) A recent authoritative review by the Federation of American Societies for Experimental Biology does not support the opinion that most dietetic foods are a necessity to the diabetic diet. Despite the lack of experimental evidence of efficacy in the dietary management of chronic disease or the maintenance of weight in the normal individual, some attention must be given to the strong preponderance of practitioners' opinion that favors the use of nonnutritive sweeteners in weight reduction or treatment of diabetes.

(6) Although the data are not conclusive, they indicate that saccharin may have potential as a noncariogenic substitute for sugar. It may have a bacteriostatic effect and may lead to reduced plaque formation in the short term, but its noncariogenic effect has not been studied clinically.

(7) There are probable benefits in making dentifrices and therapeutic drugs more palatable in order to promote their proper use.

(8) Substitution of sugar for saccharin in snack foods and possibly in soft drinks, should it occur, can be expected to lead to an increased incidence of dental caries.

(9) There are varying estimates and only limited data to indicate the extent to which sugar would be substituted for saccharin, should saccharin become unavailable. From 1969 to 1970, there was a decrease in the per capita use of nonnutritive sweeteners that reflected the ban on cyclamates. This was not followed by a measurable change in the rate of increase of the use of nutritive sweeteners. In addition, the association of increased sugar consumption with obesity or related health problems is unclear.

Regarding psychological implications:

(1) Human beings have a strong desire for sweets. Available evidence does not indicate the extent to which this represents a combination of an innate biological need and an acquired preference.

(2) Public opinion polls suggest a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. Therefore, if saccharin were removed from the market, a significant segment of the population may experience psychological stress of a transient or long-term nature. Some special groups, e.g., juvenile diabetics, may be

particularly affected if low-calorie foods and beverages that permit them a more normal lifestyle are removed without suitable replacement. At this time, the committee is unable to evaluate the implications of such psychological reliance on saccharin.

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CHAPTER 1

HISTORICAL PERSPECTIVE

Saccharin, the oldest nonnutritive sweetener in the American food supply, was synthesized accidentally by two American chemists, Fahlberg and Remsen, at the Johns Hopkins University in 1879 (Fahlberg and Remsen, 1879). Initially, it was used as an antiseptic and a preservative to retard fermentation in foods. However, its potential as a sweetening agent was soon recognized, and until recently saccharin was considered to be the sweetest substance known. It is 200 to 700 times sweeter than sugar--its taste can be detected at a dilution of 1 in 100,000--but in concentrations exceeding 0.1%, its taste is bitter (Newbrun, 1973).

By 1907, saccharin was being used in the United States as a substitute for sugar in canned products. In Europe, the consumption of saccharin increased noticeably during the two World Wars due to a scarcity of sugar (U.S. Department of Health, Education, and Welfare [USDHEW], 1977b). Despite its potency as a nonnutritive sweetener, its use, especially for cooking purposes, was somewhat limited because of its bitter aftertaste and heat lability. However, the introduction of cyclamates in the 1940's and the development in the 1950's of a variety of dietetic foods containing a mixture of cyclamate and saccharin stimulated the growth of the nonnutritive sweetener industry (Schrogie, 1970).

In 1969-1970 the ban on cyclamates rejuvenated an interest in the use of saccharin alone. By that time, saccharin was the only nonnutritive sweetener on the FDA list of substances "generally recognized as

safe" (GRAS). Since 1971, the annual per capita use of saccharin has increased steadily in the United States. In 1977, the U.S. Department of Agriculture (USDA) estimated the per capita consumption to be approximately 4.1 kg (sugar sweetness equivalent), approximately 6% of the total sweeteners in the American diet (USDA, 1978). Currently, saccharin is used predominantly in diet soft drinks (58% of the total saccharin used in 1976), as a tabletop sweetener (approximately 24% of the total saccharin used in 1976), and to a lesser extent in dietetic foods (Calorie Control Council, April 1978, unpublished data). It is also used as a sweetening agent in wine, tobacco, and drugs, in industrial processes, and in a variety of cosmetic and toiletry products (USDHEW, 1977b). In 1976, the FDA reported that approximately 2.7 to 3.5 million kg of saccharin was used in the United States. Approximately 70% of that amount was used in foods and beverages (USDHEW, 1977b). The Sherwin-Williams Company is the sole producer of saccharin in the United States. In addition, approximately 1.3 million kg is imported annually, mainly from Japan and Korea (U.S. International Trade Commission, 1977).

There are no reliable estimates of saccharin consumption, especially for the highest levels ingested. On the basis of estimates of the total saccharin used in foods and beverages in 1976, the daily per capita consumption of saccharin in the United States can be calculated to be approximately 32 mg (USDHEW, 1977b). Public opinion surveys (Harris, 1977; Market Facts, Inc., 1978) estimated that from 25% to 40% of the population uses saccharin to some degree. Further details concerning the consumption of saccharin are presented in Chapter 2.

RECENT AMERICAN AND INTERNATIONAL REGULATIONS GOVERNING SACCHARIN

The United States

In the United States, saccharin was approved for use in foods under the 1958 Food Additives Amendment to the Food, Drug, and Cosmetic Act. Under the provisions of this amendment, saccharin was included among some 600 substances that had been in use prior to 1958 and that had been accorded GRAS status. In 1972, because of questions about the safety of saccharin, the FDA removed it from the GRAS list (USDHEW, 1972b). Pending completion of chronic toxicity studies, the FDA issued an interim food additives regulation to permit continued limited use of saccharin (USDHEW, 1972a).

The FDA recommended limiting the use of saccharin to 1.0 g/day for adults. This is similar to the level recommended by the National Academy of Sciences, National Research Council (NAS/NRC) Committee on Food Protection (1955), and the NAS/NRC Ad Hoc Subcommittee on Nonnutritive Sweeteners of the Committee on Food Protection (1970).

The World Health Organization

In 1967 the Joint FAO/WHO (Food and Agriculture Organization/ World Health Organization) Expert Committee on Food Additives adopted an unconditional Acceptable Daily Intake (ADI) for saccharin of 5 mg/kg and a conditional ADI (for dietetic foods only) of 15 mg/kg. It proposed an ADI of 5 mg/kg on the basis of a no-effect level of 1% saccharin (500 mg/kg of saccharin daily) in the diets of rats. This amounted to a safety factor of 100:1 (WHO, 1977). At a meeting in Rome in April 1977, the FAO/WHO committee reviewed recent toxicological studies on saccharin, abolished the unconditional ADI, and recommended

a temporary ADI of 0 to 2.5 mg/kg until further testing could be completed (WHO, 1977).

Canada

In Canada, saccharin and cyclamates have been used for many years in low calorie foods. Under the Food and Drugs Act and Regulations of Canada these foods must bear a label indicating their low sugar and low calorie content. Since 1969 cyclamates have been banned from foods in Canada, but they can be obtained as an over-the-counter drug product (Canadian Health and Welfare Ministry, 1977). On March 9, 1977 the Health Protection Branch of the National Health and Welfare Ministry of Canada issued a bulletin banning the use of saccharin in beverages (effective July 1, 1977), in foods (from November 1, 1977), as a sweetening agent in drugs (from December 31, 1978), and in cosmetics and toothpaste (from December 31, 1979). Since September 1, 1977, the sale of saccharin in Canada has been restricted to a single-ingredient drug or saccharin in combination with cyclamates. Before the restriction on saccharin, approximately 205,000 kg of saccharin annually or 24 mg per capita daily were consumed by Canadians.

Other Countries

There is relatively little information on the use of saccharin in other countires. In 1976, the total consumption of saccharin in Sweden was estimated to be approximately 13,000 kg or 5 mg per capita daily. In October 1977, Sweden (Albanus, 1978) proposed limitations on the use of saccharin in juices and soft drinks; prohibition of its use in breads, baked goods, and fruit juices; and labeling of packages that contain saccharin. These proposals had not been adopted as of

October 1978. In Norway, saccharin is permitted only in such dietetic products as soft drinks, juices, and fish, with limitations on the amount per kilogram that is used in each product. The sale of saccharin as a tabletop sweetener is limited to drug stores (Norwegian Ministry of Social Affairs, 1978). In Japan, saccharin is regulated under the Food Sanitation Law of the Ministry of Health and Welfare (Asano, 1978). According to Section 7 of this law, standards pertaining to saccharin were developed on December 28, 1959. Although the law limits the amount of saccharin per kilogram of food, it permits the addition of saccharin to chewing gum, beverages, ice cream, jams, flour paste, cake, cookies, sauces, vinegar, processed seaweed, and processed fish.

INVESTIGATIONS OF THE SAFETY OF SACCHARIN

Concern about the safety of saccharin is not new. It was the subject of repeated investigations during the last century. However, reliable evidence concerning its toxicity has been slow to appear, and when it has, it has created frequent controversy among scientists.

In 1886, the toxicity of saccharin was tested in European workers by administering single doses of up to 5 g. In 1888, a French scientist gave diabetics 5 g doses daily for 5 months (USDHEW, 1977b). The results showed no ill effects that were considered to be of serious consequence (USDHEW, 1977b). In the following decade, sporadic reports associated loss of appetite and gastrointestinal disturbance with the ingestion of saccharin.

The simplicity of the early testing techniques is highlighted in one colorful event in the long history of saccharin. According to the Hastings Center Report (Levine, 1977), Harvey Washington Wiley (Chief

Chemist, Department of Agriculture) in 1902 formed "a poison squad" of 12 volunteers to test numerous ingredients, some of which were suspected to be poisonous, in foods. The volunteers were required to ingest the substance under examination. The resulting ailments formed the basis of judgment about toxicity. After one such testing Wiley recommended to President Theodore Roosevelt that saccharin should be banned because it was "highly injurious to health." However, the President, as the story goes, exclaimed angrily, "You say saccharin is injurious to health? Why, Doctor Rixey gives it to me every day. Anybody who says saccharin is injurious to health is an idiot." Thus, saccharin survived the first effort to ban it. In 1912 saccharin was in fact banned from foods (Knisbacher and Dodge, 1978), but during World War I, the reduction in sugar supplies prompted the lifting of the ban.

Between 1920 and 1950, numerous attempts were made to study the toxicological effects of saccharin in laboratory animals. These studies were of shorter duration and the findings did not generate concern about toxicity (USDHEW, 1977b). One of the earliest studies of chronic toxicity of saccharin was conducted in 1951. Fitzhugh et al. (1951) fed various dietary levels of saccharin to rats and reported the appearance of lymphosarcomas in seven animals that had received a 5% saccharin diet. However, these results were not considered conclusive because control animals also had a high incidence of tumors (USDHEW, 1977b).

In 1955, the NAS/NRC Committee on Food Protection reviewed the scientific evidence pertaining to the safety of saccharin and concluded that the "maximum probable tolerance level for saccharin in the human diet is...at least as great as 1.0 g per day." It further concluded that "the maximal amount of saccharin likely to be consumed is not

hazardous." The latter conclusion was based on the substitution of saccharin for the average daily consumption of sugar in the United States, which would amount to approximately 0.3 g of saccharin.

From 1960 to 1967, the use of saccharin alone and in combination with cyclamates led to an overall increase as well as significant changes in the consumption of nonnutritive sweeteners. At the request of the FDA, the NAS/NRC Ad Hoc Committee on Nonnutritive Sweeteners, Committee on Food Protection (1968) reevaluated the safety of nonnutritive sweeteners. It concluded that an intake of 1 g or less of saccharin per day by an adult should present no hazard and that 15 mg/kg of body weight per day is unlikely to be consumed. The committee also recommended further study on the basis that the existing studies on carcinogenesis, as judged by current standards, were outmoded.

The 1969 ban on cyclamates prompted new interest in saccharin because of an anticipated increase in its use. Another NAS/NRC ad hoc subcommittee of the Committee on Food Protection (1970) reviewed the available toxicity data on saccharin. Its conclusions were similar to those issued in the 1955 and 1968 NAS reports, i.e., that a total intake of 1.0 g of saccharin per day or 15 to 20 mg of saccharin per kilogram of body weight in adults who weighed between 50 to 70 kg was safe. In addition, the subcommittee recommended further study of chronic toxicity in two species in accordance with modern protocols, epidemiologic studies with emphasis on diabetics and on the relationship of saccharin to pregnancy, comparative metabolic studies in humans and in animals, and exploration of toxicologic interactions with other selected chemicals.

In the 1970's, two-generation, chronic toxicity in animals was studied by giving them multiple doses of saccharin. Among these studies,

one by the Wisconsin Alumni Research Foundation (WARF, 1972) indicated an increased incidence of bladder tumors in male rats, especially in the second generation. Because of the preliminary results of this study and of general questions about safety, the FDA removed saccharin from the GRAS list. Then, in the February 1, 1972 issue of the Federal Register, it published regulations restricting the use of saccharin (USDHEW, 1972b). Essentially, these restrictions discouraged general use by consumers pending the outcome of further toxicological studies. Simultaneously, the FDA asked the National Academy of Sciences to conduct another review of the toxicological data on saccharin.

The Academy's report (NAS, 1974) concluded that evidence had "not established conclusively whether saccharin is or is not carcinogenic when administered orally to test animals." It emphasized the uncertainty surrounding the role of orthotoluenesulfonamide (OTS, a common impurity in commercial saccharin) in the induction of tumors and recommended a reconsideration of the question when additional data become available.

Subsequently, substantial new evidence has come to light and events have moved rapidly, especially since March 9, 1977, when the Canadian Government banned saccharin (Canadian National Health and Welfare Ministry, 1977). In 1974 the Health Protection Branch (HPB) of Canada studied the relative toxicity of saccharin and OTS in two generations of rats. The results indicated that a 5% dietary level of saccharin increased the incidence of bladder tumors in male rats, especially in the second generation. The Canadian investigators concluded that saccharin is a potential cancer-causing agent. According to the official announcement, the HPB decided to remove saccharin as an additive in processed food after consultation with the Canadian Medical Association, the Canadian Diabetic

Association, the Canadian Dental Association, and the Registrars of Pharmacy (Canadian National Health and Welfare Ministry, 1977). The decision also appears to have been based primarily on three two-generation studies (two American, one Canadian), in which the ingestion of saccharin was associated with increased incidence of bladder tumors (Canadian National Health and Welfare Ministry, 1977).

Prompted by the results of the recent Canadian study, the FDA in March 1977 announced its intention to ban saccharin under the general safety requirements of the Food Additives Amendment of 1958 and the Delaney anticancer clause of this amendment (USDHEW, 1977b). The FDA's proposal to ban, as published in the Federal Register on April 15, 1977, can be summarized as follows:

The FDA intends to:

- revoke the interim food additive regulation which permits saccharin as an ingredient in prepackaged foods such as soft drinks and tabletop nonnutritive sweeteners;
- review applications for marketing saccharin as a single-ingredient drug, available without a prescription, but bearing a warning about the risk of cancer;
- ban saccharin as an inactive ingredient in drugs unless it can be shown to have an overriding benefit;
- prohibit the use of saccharin in cosmetics that are likely to be ingested; and
- prohibit the use of saccharin in veterinary drugs and animal feed.

The FDA's proposal was sharply criticized by the public, the food and drug industries, and numerous scientific organizations.

This led the Subcommittee on Health and Scientific Research of the Senate Committee on Human Resources to approach the Office of Technology Assessment (OTA) in March 1977. The OTA was asked to study the technical basis of the FDA's proposal and to report within 60 days. On June 7, 1977, the essential findings of the OTA were presented and discussed at a hearing held before the Subcommittee on Health and Scientific Research (U.S. Congress, 1977a). According to the report, which was issued in October 1977, the OTA concluded that "laboratory evidence demonstrates that saccharin is a carcinogen" and that "evidence leads to the conclusion that saccharin is a potential cause of cancer in humans." It further concluded that "because of its widespread use, the availability of a nonnutritive sweetener is of perceived psychological benefit to many people" and that "whether or not using a nonnutritive sweetener leads to measurable health benefits has never been tested" (U.S. Congress, 1977b).

Mounting public and congressional concern about the fate of saccharin is evident from numerous bills introduced in the House and the Senate since the FDA's announcement of the ban in March 1977. Finally, on November 3, 1977, The Saccharin Study and Labeling Act (PL 95-203) was enacted, (U.S. Congress, 1977c). This Act required that the Secretary of Health, Education, and Welfare ask the National Academy of Sciences to conduct "studies concerning toxic and carcinogenic substances in foods, to conduct studies concerning saccharin, its impurities and toxicity, and the health benefits, if any, resulting from the use of nonnutritive sweeteners including saccharin." It prohibited the Secretary of HEW from implementing the proposed ban on saccharin for a period of 18 months, but required that food products containing saccharin bear a warning on the label. In addition to an evaluation of saccharin, the Act calls upon

the National Academy of Sciences to study and develop policy recommendations concerning the safety of the nation's food supply.

Since this study has been in progress at the Academy, representatives of the affected food and beverage industries (Gelardi, 1978), the FDA, and the National Cancer Institute (USDHEW, 1977a) have announced their intention to conduct additional investigations into the carcinogenic potential of saccharin.

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CHAPTER 2

CONSUMPTION OF SACCHARIN

The extent of exposure to a substance is a significant determinant of the degree of risk or the magnitude of benefit. As such, an understanding of the patterns of consumption of saccharin is of particular relevance to this report.

Although saccharin has been consumed by humans since the late 19th Century, reliable information about the prevalence of use, the demographic characteristics of the users, and the frequency and amounts of saccharin consumed has been scarce. Often, estimates of per capita use are extrapolated from data on the total amount of saccharin that has been produced in the United States plus the quantity that has been imported, i.e., "disappearance from the market data." Little attempt has been made to determine the relevance of such estimates for special population groups such as diabetics. The limited information available on the direct consumption of saccharin has been based on surveys of small and perhaps unrepresentative samples of the population.

In an effort to draw a more meaningful profile of the use of saccharin, the National Academy of Sciences (NAS) contracted with the Market Research Corporation of American (MRCA), as it had in 1974 (NAS, 1974), to obtain data concerning the direct consumption of saccharin (MRCA, 1978a,b). The information that was gathered by MRCA was based on a 2-week menu diary that was kept by a consumer panel of 4,000 households (>12,000 individuals). To estimate the use of saccharin, the committee compared these data, whenever applicable, with information from a public opinion poll of nearly 1,500 individuals, which was conducted by Market Facts Incorporated (MFI,

1978).[1] It also made comparisons with data collected by the National Center for Health Statistics during the years 1971-1974 (U.S. Department of Health, Education, and Welfare [USDHEW], 1978), the Household Food Consumption Survey conducted by the U.S. Department of Agriculture in 1965-1966 (USDA, 1972, 1978a), and a National Family Opinion survey (NFO, 1967), which was conducted for the Pillsbury Company.

This chapter contains a rough description of the use of saccharin in the United States based on these data. Caution should be exercised when interpreting these data since much of the information was derived from surveys whose purpose was to measure the size of the market for noncaloric foods and not nutrient intake.

THE PRODUCTION AND GENERAL USE OF SACCHARIN

Often, disappearance data are equated with ingestion figures. However, actual consumption is somewhat lower due to nonfood use, wastage, spoilage, or spillage. Furthermore, disappearance data are not adequately adjusted for discrepancies in user-consumer inventories. Therefore, when comparing disappearance data with consumption, one should assume the loss of a certain percentage (perhaps as high as 20%).

In the United States the use of saccharin in foods has risen from 0.6 million kg (1.3 million lbs) in 1961 to 2.9 million kg (6.4 million lbs) in 1977 (Table 2-1), an increase of 385%, or 23% per year. There was a plateau in this use between 1970 and 1973, following the cyclamate ban.

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[1] For a discussion of the methodology used in the MRCA and MFI surveys, see page 2-16.

TABLE 2-1

Production, Imports, and Uses of Saccharin from 1961 to 1977 in Million Pounds

Year	Domestic Production	Imported[a]	Total	Used in Food[b]	Used in Other Products[c]
1961	NA[d]	0.2[e]	1.6	1.3	0.3
1962	NA	0.5[e]	1.9	1.6	0.3
1963	1.4[e]	1.1[e]	2.5	1.8	0.7
1964	2.4[e]	0.8[e]	3.2	2.2	1.0
1965	2.5[e]	0.8[e]	3.3	2.5	0.8
1966	NA	NA	3.5	2.9	0.6
1967	NA	NA	3.7	3.1	0.6
1968	NA	NA	4.0	3.3	0.7
1969	NA	NA	4.4	3.7	0.7
1970	NA	NA	5.0	4.2	0.8
1971	3.4[f]	1.4[f]	4.8	4.0	0.8
1972	NA	NA	4.8	4.0	0.8
1973	2.7	2.1	4.8	4.0	0.8
1974	2.5	3.4	5.9	4.9	1.0
1975	2.8	3.1	5.9	4.9	1.0
1976	4.0	2.7	6.7	5.6	1.1
1977	4.8	2.8[g]	7.6	6.3	1.3

[a] From U.S. International Trade Commission, 1977.

[b] U.S. Department of Agriculture, 1978b.

[c] Cosmetics, pharmaceuticals, tobacco, electroplating, cattle feed, etc. (Assumed to be 20% of the total except for 1963-1965.) From Calorie Control Council, personal communication, 1978.

[d] Not available.

[e] From Ballinger, 1967.

[f] From Walter, 1974.

[g] Estimated from 9-month data from U.S. International Trade Commission, 1977.

Approximately 80% of imported saccharin originates in Japan. Smaller amounts are imported from Taiwan and Korea (U.S. International Trade Commission, 1977). Recently, imports have accounted for less than half of the saccharin used in the United States (Table 2-1). All imported saccharin is manufactured by the Remsen-Fahlberg (RF) method. Using the RF process, the Monsanto Chemical Company produced 50% of the saccharin on the U.S. market until 1972, when they ceased production of the product. Since then, all the domestically produced saccharin has been manufactured by the Sherwin-Williams Company, which uses the Maumee process. (The two manufacturing processes are described in Chapter 3.)

In general, it is assumed that 20% of all the saccharin produced and imported is used in the manufacture of such products as cosmetics, pharmaceuticals, tobacco, and cattle feed, and in electroplating and other processes. The proportion of saccharin used for food and nonfood purposes in 1976 is shown in Table 2-2 (Calorie Control Council, personal communication, 1978).

TRENDS IN CONSUMPTION OF NONNUTRITIVE SWEETENERS

It is difficult to compare data on the consumption of nonnutritive sweeteners because the information from diverse sources is not always compatible. For example, the age groups selected in the various surveys may be different, the consumption by sex may or may not be reported, and information may be solicited solely for artificially sweetened soft drinks in one case and for all foods containing saccharin in others. The frequency of use may also vary considerably (daily, once a week, etc.). Thus, the distinction between a user versus a nonuser is often an arbitrary one. Moreover, the methods of data collection can vary from a 24-hour diet-recall to 2-week food diaries. The combined use of cyclamates and saccharin

TABLE 2-2

Use of Saccharin in Foods and in Nonfood Items in the United States, 1976 [a]

Foods	Quantity used, million lbs		Percentage of saccharin used in food		Percentage of saccharin used for all purposes	
Soft drinks	2.900		58		45	
Tabletop sweeteners	1.200		24		18	
Other foods (includes fruits, premixes, juices, candy, gum, jellies, etc.	0.900		18		14	
		5.000		100		77
Nonfood Items						
Cosmetics (toothpaste, mouthwash, lipstick, etc.)	0.650				10	
Pharmaceuticals (coatings for pills)	0.455				7	
Smokeless tobacco products (chewing tobacco and snuff)	0.135				2	
Electroplating	0.130				2	
Cattle feed	0.065				1	
Miscellaneous	0.065				1	
SUBTOTAL		1.500				23
TOTAL		6.500				100

[a] Calorie Control Council, personal communication, April 1978.

(in a 10:1 cyclamate-saccharin mixture) prior to 1970 makes it difficult to estimate the amount of saccharin consumed. Hence, a considerable amount of judgment must be exercised when commenting upon the trends.

Seven studies conducted between 1965 and 1978 are compared in Table 2-3. According to the 1965-1966 Household Food Consumption Survey of the U.S. Department of Agriculture (1972, 1978a), 3% of the total population reported using artificially sweetened carbonated soft drinks.

In 1967, National Family Opinion (NFO) sampled the use of cyclamates and saccharin (in a 10:1 mixture) twice among 450 children and adolescents under age 19. These juveniles had been preselected from an earlier NFO study in which they had responded positively to a question concerning the use of nonnutritive sweeteners. Fifty-eight percent of the respondents used the saccharin-cyclamate mixture at least once in one of two 1-week periods.

The National Health Survey, which was conducted by the National Center for Health Statistics (NCHS) from 1971 to 1974, estimated that 13% of the 20,000 persons sampled used artifically sweetened cold drinks (USDHEW, 1978).

During the last 11 years, MRCA used the same method in three surveys (MRCA, 1967-1968; 1972-1973; 1977-1978) which measured the use of artificial sweeteners. Data were collected from a consumer panel composed of approximately 4,000 households. Participants completed a daily diary of all food eaten by all members of the family for 14 days. The 1967-1968 survey indicated that 11% of the 12,781 respondents used tabletop sweeteners in a 10:1 cyclamate-saccharin mixture (MRCA, 1968). In 1972-1973, 28% of all respondents used saccharin-containing products of every type (MRCA, 1978a). In 1977-1978 the proportion of saccharin users increased to 35% (MRCA, 1978b).

TABLE 2-3

Saccharin Use from 1965 to 1978

Dates of survey	Reference	Description of sample	Users, %
April through June 1965	USDA, 1972, 1978a	24-hour recall of food and nutrient intake of 14,519 individuals in the United States	3[a]
April and July 1967	NFO, 1967	450 children less than 19 years old preselected from families who reported use of artificial sweeteners (saccharin plus cyclamates)	58
July 1, 1967 to June 30, 1968	MRCA, 1968	1,000 households participating in a 2-week menu diary; 12,781 individual respondents in a 2-week menu diary (saccharin plus cyclamates)	21[b] 11[b]
1971-1974	USDHEW, 1978	Numbers of users of artificially sweetened cold drinks reported from 20,000 interviews	13[a]
July 1, 1972 to June 30, 1973	MRCA, 1978a	12,337 individuals using a 2-week menu diary	28
July 1, 1977 to March 30, 1978	MRCA, 1978b	8,415 individuals using a 2-week menu diary	35
July 12 to August 13, 1978	MFI, 1978	1,480 individuals over age 13, weighted to obtain a higher proportion of diabetics and users of sugar-free products	26

[a] Soft drinks only.

[b] Tabletop sweeteners only.

Market Facts Incorporated (MFI, 1978) conducted a survey of saccharin use on behalf of the Calorie Control Council. Responses were obtained from 1,480 individuals over age 13. This group was a weighted sample of diabetics and users of sugar-free products. MFI estimated that 26% of the total U.S. population used saccharin.

MRCA studies indicate that the use of artificial sweeteners is increasing in this country. A precise estimate of the proportion of the population using saccharin is not possible, but the surveys suggest a range of perhaps one-quarter to one-third of the total U.S. population (approximately 50 to 70 million Americans).

The MFI survey (1978) also reveals a rapid increase in the numbers of users of saccharin. The estimates in Table 2-4 were computed from the length of time that respondents had used sugar-free products. There has been an approximate doubling in the number of users every 5 years.

CONSUMPTION BY AGE AND SEX

Generally, women are greater users of saccharin than are men as reported in all surveys that provide sex-specific data. Over the years a shift appears to have occurred in the relative proportion of men and women using nonnutritive sweeteners (Table 2-5). Both the 1965 USDA (1972, 1978a) and the 1971-1974 NCHS surveys (USDHEW, 1978) indicate that women used from 50% to 100% more diet drinks than men. Two of the MRCA surveys (MRCA, 1978a,b) show that males consume saccharin about 80% as frequently as do females. In the 1972-1973 MRCA study (MRCA, 1978a), the use of saccharin seemed to be correlated with increasing age for both sexes although the differences are not great. Kessler and Clark's data, which were collected from 1972 to 1975, are in agreement with respect to the sex differences.

TABLE 2-4

History of sugar-free product consumption[a]

Length of use, years	Number of users
> 1	38,281,000
> 5	19,482,000
>10	9,399,000
>15	4,956,000

[a] Estimates based on MFI, 1978.

TABLE 2-5

Consumption of Nonnutritive Sweeteners by Sex and Age

Survey	Percent of users of artificially sweetened soft drinks, adjusted for age	Percent of users by age group, years							
USDA, 1972, 1978a		< 9	9-11	12-19	20-34	35-54	55-64	65-74	75+
Male	2	1[a]	2	1	2	2	1	1	1
Female	3		3	2	5	4	3	2	1
USDHEW, 1978			1-5	6-11	12-17	18-44	45-64	65-74	
Male	9		5	6	7	9	12	8	
Female	17		6	6	15	22	22	11	
	Percent of users of all foods, adjusted for age								
MRCA, 1978a			0-9	10-19	20-29	30-39	40-49	50-59	60+
Male	25		23	22	23	26	24	27	33
Female	31		25	26	32	35	34	35	34
MRCA, 1978b									
Male	31		36	29	29	31	29	28	31
Female	38		38	34	42	46	36	39	35
MRCA, 1978a		2	2-5	6-12	13-17	18-24	25-34	35-44	45-54	55-64	65+
Both sexes	28	13	28	25	24	25	30	29	29	35	33
MRCA, 1978b											
Both sexes	34	17	42	37	30	32	38	35	35	34	33

[a] Both sexes.

The 1977-1978 MRCA data (MRCA, 1978b) show that the highest proportion of users among males is in the youngest, i.e., 0- to 9-year, age group. For females, the greatest proportion of users is in the 20- to 39-year age group.

DAILY LEVELS OF CONSUMPTION PER KILOGRAM OF BODY WEIGHT

Table 2-6 lists four sources of data concerning the mean amount of saccharin used per day and per kilogram of body weight per day. There are inherent problems in comparing these data. The 1967 National Family Opinion survey was conducted when cyclamates were still available, and the Market Facts Inc. (1978) opinion poll was performed after the proposal to ban saccharin. The only longitudinal data are from the two MRCA surveys (MRCA 1978a,b).

One may deduce from the internally consistent MRCA surveys that between 1972 and 1978 the amounts of saccharin consumed per day and per kilogram of body weight have risen sharply in the younger age groups, especially in the ages between 2 and 24 years. The data consistently show that children consume less saccharin per day than adults; however, based on the amount consumed per unit of body weight, the younger children have a larger intake of saccharin than do older children or adults as they do for all food constituents.

From the MFI data (1978) it appears that, as previously shown, males and females consume essentially the same average amounts of saccharin.

Table 2-7 summarizes the daily consumption of saccharin by nondieters, dieters (persons on a low-cholesterol diet, low-fat diet, low-calorie diet, or other diet), and those on a diabetic diet. In general, the three MRCA surveys (MRCA 1968, 1978a,b) indicate that a significant percentage of diabetics (60% to 78%) use saccharin. They use it more frequently and in larger amounts (approximately two to three times as much) than do nondiabetics. The MFI (1978) survey indicated a still higher percentage of users among diabetics

TABLE 2-6

Milligrams of Saccharin Consumed Per Day
by Age and Per Unit of Body Weight

Survey

NFO 1967

Age group, years	All	1-3	4-6	7-9	10-12	13-15	16-18
mg/day	24.0	11.5	19.5	26.0	24.5	7.5	3.5
mg/kg/day	0.8	0.7	1.4	0.8	0.6	0.4	0.5

MRCA 1972-1973

Age group, years	All	<2	2-5	6-12	13-17	18-24	25-34	35-44	45-54	55-64	65+
mg/day	23.8	6.5	9.3	9.8	14.8	18.4	30.0	27.8	32.0	33.4	30.9
mg/kg/day	0.4	0.6	0.3	0.2	0.3	0.4	0.4	0.4	0.4	0.5	0.4

MRCA 1977-1978

mg/day	32.0	19.0	23.1	24.8	32.9	37.6	35.5	38.5	35.8	33.6	30.9
mg/kg/day	0.6	1.7	1.5	0.8	0.6	0.6	0.5	0.6	0.5	0.5	0.4

MFI 1978

Age group, years	All	13-17	18-29	30-44	45-54	55+
mg/day--both sexes	157.1	102.8	159.0	181.6	171.4	134.8
mg/day--male	162.2	NA[a]	NA	NA	NA	NA
mg/day--female	154.0	NA	NA	NA	NA	NA

[a] No data available.

TABLE 2-7

Saccharin Consumption by Type of Diet

Type of diet	Total saccharin consumed						
	MRCA (1967-68)	MRCA (1972-73)		MRCA (1977-78)		MFI (1978)	
	%	%	mg/day	%	mg/day	%	mg/day
No diet	20[a,b]	23	16.2	29	24.9	24[a]	155.1[c]
Low cholestrol	NA[c]	36	31.3	37	28.9	NA	NA
Low fat	NA	38	30.2	30	37.9	30[d]	NA
Low calorie	NA	43	32.5	51	40.3	NA	NA
Other diet[e]	NA	33	23.4	37	30.6	NA	NA
Diabetic	60[b]	65	56.7	78	53.8	91	173.1

[a] Excludes diabetics, but may contain other types of diets.

[b] Tabletop sweeteners only--percent of diabetic households.

[c] No data available.

[d] Percent of use among those who responded that they were either severely overweight (25 lbs or more over ideal weight) or overweight.

[e] Includes the following diets: allergy, bland/soft, high calorie, high protein, low protein, low salt, and other unspecified diets.

(91%) than did the MRCA surveys. In addition, 1972-1973 and 1977-1978 MRCA surveys (MRCA, 1978a,b) show that the percentage of users among nondieters and the mean daily intake of saccharin appear to have increased during this 5-year period.

These data are consistent with other reports on diabetics. A 1970 study in The Netherlands reported that 73% of 1,593 diabetic respondents used artificial sweeteners and that there was higher use among women than men (Aardenhout, 1969). From a survey of members of the British Diabetes Association, Armstrong et al. (1976) reported that 67% of males and 55% of females used saccharin tablets daily. A survey of hospital patients indicated that 64% of male diabetics used saccharin, compared to 48% of the female patients (Armstrong and Doll, 1975). The MRCA and MFI data disclose few differences in the proportions of female and male diabetic users of saccharin.

An examination of the sources of foods that contain saccharin (Table 2-8) shows clearly that the most abundant saccharin-containing products are soft drinks and that consumption of them has increased between the two MRCA surveys (1972-1973; 1977-1978). From 1972 to 1978 the proportion of users grew by 10%, while the amount of saccharin used increased by 55%. Of the total amount of saccharin consumed, soft drinks accounted for 58.5% in 1972-1973 (MRCA, 1978a) and for 66.9% in 1977-1978 (MRCA, 1978b). The use of tabletop sweeteners declined from 34% in 1972-1973 to 27.1% in 1977-1978. Overall, there has been a 36% increase in the total use of saccharin in 5 years. Of the actual increase, 90% can be attributed to the increased consumption of soft drinks.

If, over 12 months during 1972-1973, 92,526 mg of saccharin were consumed by 12,337 respondents (MRCA, 1978a), then the 1972 U.S. population can be estimated to have ingested 574,875 kg of saccharin. This is

TABLE 2-8

Amount and Percent of Saccharin Consumed by MRCA respondents, by Type of Food

Food	Saccharin MRCA 1972-1973[a] N = 12,337 mg	%	MRCA 1977-1978[b] N = 8,415 mg	%
Yogurt	218	0.2	NA[c]	NA
Chocolate drinks, whipped topping	48	0.1	181	0.2
Ice cream, ices	1,191	1.3	511	0.5
Pudding	74	0.1	210	0.2
Juice substitutes, breakfast drinks	1,333	1.4	1,173	1.2
Soft drinks	54,153	58.5	63,151	66.9
Fruits	760	0.8	196	0.2
Jello	780	0.8	533	0.6
Salad dressing	393	0.4	201	0.2
Fruit toppings, syrup	238	0.2	68	0.1
Jelly	624	0.7	330	0.3
Chewing gum	17	0.0	23	0.0
Iced-tea mix	1,276	1.4	2,233	2.4
Tabletop sweetener	31,421	34.0	25,555	27.1
TOTAL	92,526	99.9	94,365	99.9

[a] 12 months.

[b] 9 months.

[c] No data available.

equivalent to 1,264,725 lbs, about one-third the amount used in food production during 1972 as estimated in a 1974 NAS report (3.7 million lbs) (NAS, 1974). The 1977-1978 MRCA data (MRCA, 1978b) showed that over 94 g were consumed by 8,415 respondents. This can be extrapolated to a total consumption of 900,476 kg of saccharin per year in the United States. This is about 2 million lbs in food products, about 40% of the 5 million lbs (2.3 million kg) estimated by the Calorie Control Council for 1976 (Calorie Control Council, personal communication, 1978). In contrast, when the MFI (1978) consumption data are extrapolated to the U.S. population over 13 years of age, they approximate closely the amounts in food that were calculated by the Calorie Control Council (personal communication, 1978). This is surprising since disappearance data are not adjusted for waste and are generally overestimates of consumer use.

Other Social and Economic Variables

The MRCA data (MRCA, 1978a,b) also contained information on the use of saccharin and saccharin-containing products by race, income, city size, education, and geographic region of the United States. In addition, the following percentiles of use of saccharin were also obtained for each of these variables: 50, 90, 95, 97.5, 99, and 99.5. For the sake of brevity this additional information is not being reviewed. However, all consumption data that were gathered by the committee are being delivered to the Food and Drug Administration for its use.

METHODS USED FOR MFI AND MRCA ESTIMATES

The methods used by MFI (1978) and MRCA (1977-1978) to estimate saccharin intake differ, although both started with the same information. The Calorie Control Council provided the two organizations with the number of

milligrams of saccharin in food products, but each used a different algorithm to arrive at an average consumption figure.

Since MRCA did not ask the respondents to report the quantity consumed per serving or how many servings they ate, these were estimated from age-specific data that had been collected by the USDA in 1965 (USDA, 1972). The amounts of saccharin consumed were calculated by summing the milligrams of saccharin per gram of food for each meal and snack over 2 weeks and then dividing the total by 14 days to obtain an average daily intake. For example, if a 25-year-old MRCA respondent recorded that he drank a diet cola six times during the 2-week menu census period, then he is counted as having drunk 45.71 mg/day. This was calculated by multiplying the concentration of saccharin (mg/g) in the product by the 1965 average amount (g) of the specific food consumed by age[1] times the number of eating occasions. This total was then divided by 14 days:

$$\frac{0.3548 \text{ mg/g} \times 279.6 \text{ g} \times 6 \text{ drinks}}{14 \text{ days}} = 45.71 \text{ mg/day}$$

This method is liable to underestimate the amount of saccharin consumed because there are no measures of actual intake by the respondent; it is not known if the 1965 estimates of serving size accurately reflect intakes during the 1970's; and it is likely that snacks and foods eaten away from home are underreported.

In contrast, MFI asked its respondents to provide a 24-hour recall of their use of foods containing saccharin. The amounts of saccharin were estimated by multiplying the milligrams per ounce or fluid ounce by a specified serving size. MFI recorded fractions of servings as whole

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[1] Age groups used were: <2, 2-5, 6-12, 13-17, 18-24, and ≥ 25.

portions, e.g., for beverages, any amount under 12 oz was counted as 12 oz, from 13 to 23 oz was counted as 24 oz, etc. In other words, each portion was rounded upward to the next highest specified serving size. In addition, the survey was conducted in July and August when intake of cold fluids such as diet drinks was likely to be high. These two aspects of the MFI survey would lead to overestimates of the amounts of saccharin consumed.

In this light the two surveys provide only a range of daily intakes and must be interpreted with caution.

SUMMARY

The committee does not wish to draw definitive conclusions from these data, but directs attention to the following apparent trends:

(1) The percentage of the population consuming saccharin-containing foods and the amounts consumed are both increasing. The percentage of young children that consume saccharin is also rising. Young children consume fewer total milligrams per user than do older persons, but the amount per unit of body weight often surpasses the intake among adults, the same as one would find with other food components. A major problem remains in interpreting these data: does the increase in saccharin consumption add to or replace sugar or other calorie consumption? The consideration of both risks and benefits will be influenced by the answer to this question. The committee recommends that further research be performed on consumption patterns.

(2) Whereas the percentage of women consuming saccharin was once considerably higher than the percentage of men, the margin of difference between the sexes has narrowed.

(3) Data indicate that the greatest users are now females in the child-bearing years (20- to 39-year age group) and males from birth to 9 years of age.

(4) Sixty to 90% of all diabetics (or those who classify themselves as diabetics) use saccharin extensively. A greater proportion of dieters (on low-calorie, low-cholesterol, low-fat, and other diets) consume saccharin than do nondieters.

(5) Soft drinks are the most frequently consumed saccharin-containing products on the market. They account for 90% of the increased consumption of the sweetener.

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CHAPTER 3

RISK ASSESSMENT OF SACCHARIN AND ITS IMPURITIES

LABORATORY INVESTIGATIONS

The greatest concern regarding saccharin consumption is the risk to humans of cancer. Thus, the following background information on chemical carcinogenesis is presented to facilitate the understanding of the findings that are described later in this chapter.

Cancer in animals and in humans can be induced by a number of different kinds of chemicals, both man-made and naturally occurring. Of these, polycyclic aromatic hydrocarbons, aromatic amines, nitrosamines and nitrosamides, nitroquinolines, nitrofurans, and mycotoxins are among those that have been studied most thoroughly.

Even with the most active carcinogenic chemicals, the process of cancer development is slow, requiring the equivalent of one-quarter to one-half of the average lifespan of the species. For example, in rodents from 6 to 24 months may be required to produce cancer whereas in humans 15, 25, 30 years, or even longer may be needed. Continual exposure to a carcinogen for such periods is often not necessary, even for a maximum incidence of cancer. In skin, liver, mammary glands, colon, and, probably, in most other tissues or organs in laboratory animals, carcinogenesis can be induced by a brief exposure to one type of chemical, an initiating carcinogen, followed by a prolonged exposure to other chemicals, called promoting agents or promoters. Promoters are

often not able to initiate carcinogenesis by themselves or they do so very inefficiently. At best, they are carcinogens of low potency. Most carcinogens are capable of both initiating and promoting and, thus, can produce cancer by themselves after repeated or prolonged exposure.

The apparent latent period between initiation and the appearance of cancer is not a true latent period. Rather, it is characterized by the presence of new cells that represent steps or stages in the slow cellular evolution from normal, through initiated, preneoplastic, and premalignant cells, to the ultimate malignant cells that characterize cancer. Generally, the new cells in the early phases grow quite slowly. They may have distinctive structural and biochemical markers that facilitate their identification with reasonable certainty. In humans, these lesions have been studied most thoroughly in the cervix and in the skin but now are receiving greater attention in the urinary bladder, breast, and respiratory tract, among other sites.

The process of promotion appears to be essential for cancer development. For example, in tissues such as the skin and liver, changes in cells or tissues that have been induced by a brief exposure to a carcinogen may persist for most of the lifetime of an animal without undergoing further steps in the carcinogenic process. The essentially irreversible nature of the initiating events emphasizes the potential hazard for cancer development from even a brief exposure to a potent carcinogen.

In contrast to initiation, many of the events that occur

during the process of promotion and prior to the appearance of cancer appear to be reversible. The focal collections of altered cells that proliferate during the several steps and that fall under the general phenomenon of promotion may disappear with discontinuance of the promoting stimuli. Thus, for many chemicals, a continual exposure to a promoting environment over a relatively long period seems to be required for the development of cancer.

The essential nature of the process of promotion is not understood. There is general agreement that a stimulus for cell proliferation is one component. However, this by itself is insufficient. Although the analysis of promotion is largely undeveloped, it appears that each organ or tissue may require its own special type of environment in order to select and encourage the growth and further evolution of those few cells that are altered during initiation. For example, croton oil and one group of its active derivatives, the phorbol esters, are potent promoters for the skin, phenobarbital for the liver, bile acids and cyclopropenoid fatty acids for the colon, and prolactin and other hormones for the mammary gland. If this organ-specificity proves to be a general phenomenon in promotion, it poses major problems in the development of suitable general assay procedures for promoters and of appropriate guidelines for wise government regulation.

Another aspect of carcinogenesis that requires attention is the existence of cocarcinogens. These compounds or agents enhance the development of cancer that is caused by other sub-

stances. For example, asbestos workers or uranium miners have little if any risk of developing lung cancer if they do not smoke, but have a very greatly increased risk over other segments of the population if they do smoke. It is not understood whether this so-called cocarcinogenic effect enhances initiation, promotion, or both.

The susceptibility to the effects of carcinogens in animals and, apparently, also in humans varies considerably with the time of exposure in relation to the period of normal development. Since embryologic and fetal development are characterized by vigorous cell proliferation, and since proliferating cells appear to be at far greater risk to carcinogens than are quiescent cells, fetuses of pregnant females are particularly vulnerable to carcinogens.

An outstanding recent example of this is the development of genital cancer in 18- to 25-year-old women whose mothers had received diethylstilbestrol during pregnancy. Also, even a brief exposure of laboratory animals to some carcinogens during pregnancy (transplacental exposure) can result in a very high incidence of brain tumors in the offspring many months after birth. Similarly, adult organs or tissues in which there is usually no cell proliferation, e.g., the liver, pancreas, and urinary bladder, are placed at a greater risk if injury is induced either by the carcinogen itself or by some other injurious agent. This might be of importance in explaining some of the effects of saccharin, as outlined below.

Most carcinogenic agents require metabolic conversions to active derivatives, most often highly reactive compounds called

"electrophilic reactants". These active chemicals can interact with many different cell constituents including deoxyribonucleic acid (DNA), ribonucleic acids (RNA), and proteins. Some of these interactions, especially some of those with DNA, are believed to have special relevance to the initiation of cancer development. In some instances, DNA repair processes play an important role in modulating the initiation events produced by carcinogens.

Alterations in cellular macromolecules, especially DNA, are thought to be the basis for the majority of short-term tests for potential carcinogens. Mutagenesis, chromosome damage, and other genetic effects of the activated forms of carcinogens are a reflection of the damage to DNA. Only cells that can convert metabolically the parent compound to the ultimate carcinogen would be expected to be suitable targets in a short-term assay. For cell lines that are devoid of activation and that are used in short-term assays, an enzyme preparation from liver, either from an animal or a human, is added to the system to carry out the activation process. The active product(s) then interact with the appropriate sites in the bacteria or other types of cells that are the test species.

In a few test systems, mammalian cells are used to provide a more complex end-point, "cellular transformation". The response of this system resembles cancer in many ways, and in some instances is believed to be a predictive surrogate test assay for carcinogenesis in vivo, provided that the assay includes reimplantation of transformed cells into the syngeneic host. Here again, an activating system is required if the requisite metabolic activation of the particular type of carcinogen is missing in the test organism or cell.

The presence and intensity of metabolic conversion to active or ultimate carcinogens varies widely among tissues and, in the same tissue, from species to species. This variation is an important factor in determining both the tissue or organ specificity of a carcinogen as well as the species specificity.

However, the levels of metabolic activity in many cells or tissues are subject to major modulations by nutrition, drugs, and toxic agents as well as by hormones and age. These types of modulations may well be important in explaining some of the variations in target organ specificity within any one species or between species. Thus, for example, a carcinogen, such as 2-acetylaminofluorene, which induces mostly liver cancer in one species with one dietary regimen, may induce urinary bladder cancer when the compound is given with another dietary regimen. Many carcinogens induce one spectrum of cancers in one species and a different spectrum in another species. Such differences in organ response to a single carcinogen are quite common with several types of chemical carcinogens.

Since the metabolic pattern of organs or tissues and their responses to acute injury are often very similar among different species, it is not surprising that chemicals that are shown to be carcinogenic in one species often show the same type of response in other species. This relative "unity of biology" forces us to assume <u>in principle</u> the validity of qualitative extrapolation of toxic effects of chemicals from animals to humans, unless adequate data on humans preclude this method of hazard assessment. However, given the many factors that modify chemical-induced carcinogenesis,

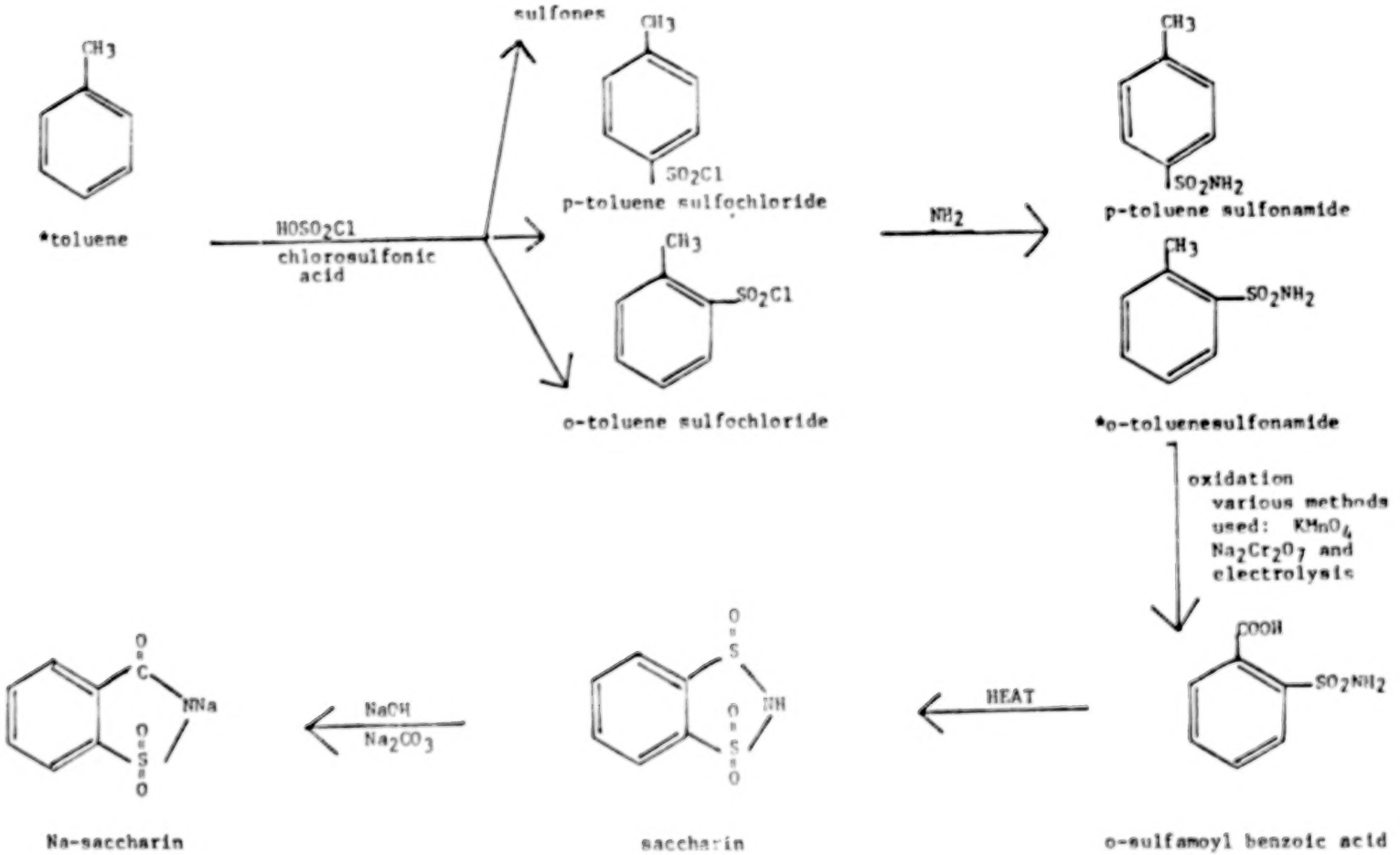
the direct extrapolation at a quantitative level is fraught with many uncertainties.

Genetic background is an important consideration when determining the susceptibility of different individuals within any one species. Increasing experience with humans, backed by considerable evidence from studies with laboratory animals, points clearly to the existence of major genetic-based differences in susceptibility (estimated to be at least 30-fold [Harris et al., 1978]) to the chronic toxic effects of chemicals. This poses a problem for humans, since some humans will be highly susceptible or highly resistant to a particular toxicant. Can appropriate safeguards be devised to protect the majority of the susceptible individuals? Clearly, new technologic approaches to the identification of high risk individuals will be required in developing guidelines for their safety.

Experimental Findings--Saccharin

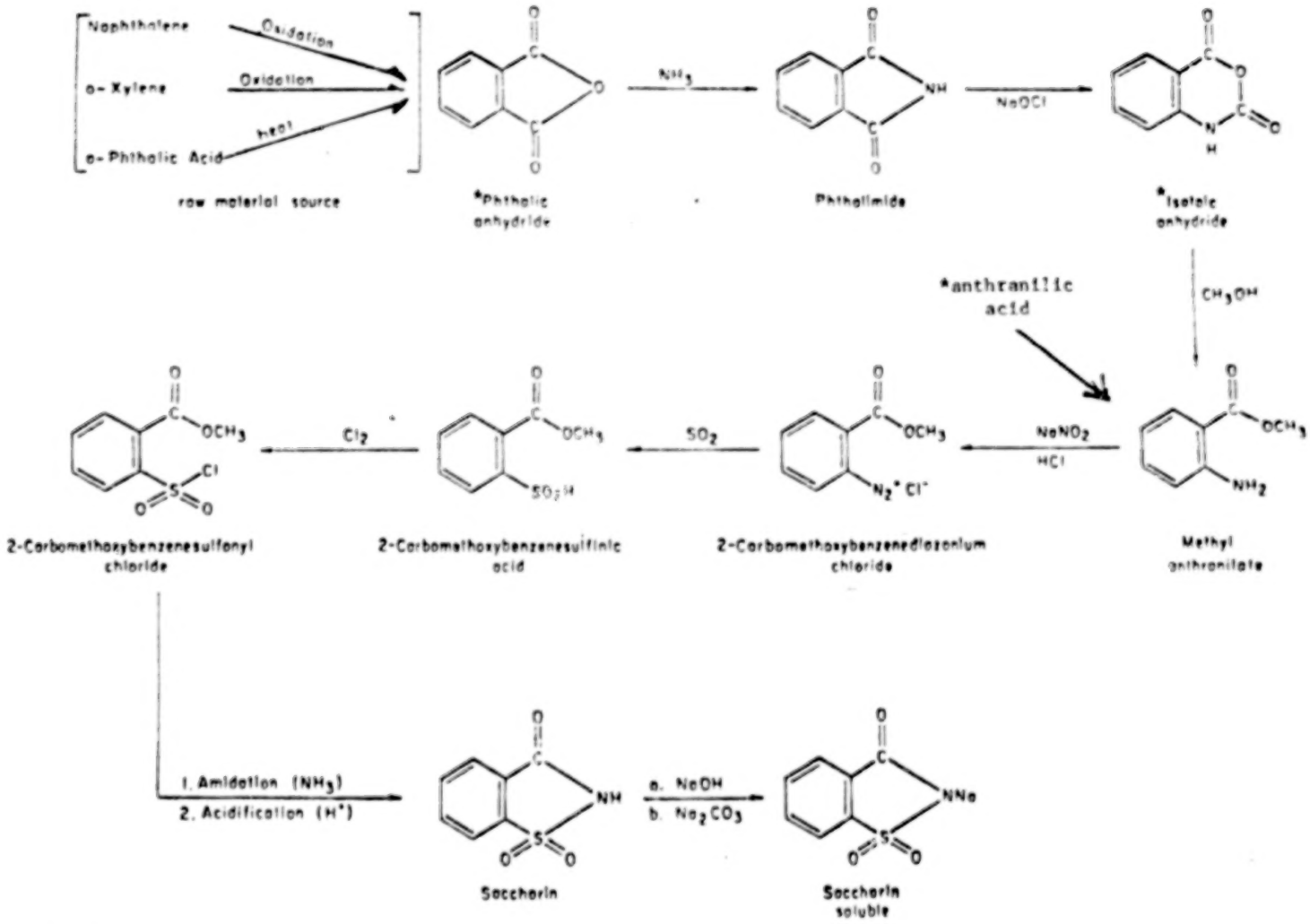
Chemistry. Saccharin (1,2-benzisothiazol-3(2H)-one 1,1-dioxide) is manufactured by two different processes. One older method, known as the Remsen-Fahlberg (RF) process (Remsen and Fahlberg, 1879), is shown in Figure 3-1. A more recent method, the Maumee process, is shown in Figure 3-2. Certain details of these processes are proprietary information of the individual manufacturers; therefore, they are not included in the figures.

The RF process may use either toluene or orthotoluenesulfonamide (OTS) as the starting material (Munro et al., 1975a; Stavric et al., 1978; Stavrik, personal communication). When toluene is used, the initial reaction is sulfonation followed by amida-



*Starting points in manufacture.

FIGURE 3-1. Remsen-Fahlberg Manufacturing Process.



*Starting points in manufacture.

FIGURE 3-2. Maumee Manufacturing Process.

tion to yield OTS. The OTS is then oxidized to the acid ortho-sulfamoylbenzoic acid. This product is hydrolyzed to saccharin which may be converted to any of several saccharin salts. This process produces characteristic impurities which may differ somewhat, either qualitatively or quantitatively, as a result of elected variations in the process (e.g., one of three different oxidizing agents may be used) or by the introduction of unintentional variations (e.g., a very small temperature fluctuation which may cause the introduction of sulfone by-products during the sulfonation of toluene). Some of the impurity variation found in different lots of saccharin that have been produced by the same manufacturer are due to limited technical control which introduces such unintended variations.

The principle impurity in RF-manufactured saccharin is OTS, which, until 4 to 5 years ago, was present in commercial samples in concentrations as high as 5,000 ppm. More recent refinements, either in manufacture or purification, in the RF process have yielded commercial preparations with as low as 25 ppm OTS.

The Maumee process (E. D. Compton, Sherwin-Williams Co., personal communication; Munro et al., 1975b), starts with either phthalic anhydride or anthranilic acid (Munro et al., 1975b). Phthalic anhydride is converted in a three-step process to methyl anthranilate. This product is then converted to the diazonium salt and sulfonated to give the corresponding sulfinic acid (2-carbomethoxybenzenesulfinic acid). Subsequent chlorination and amidation yields saccharin. If anthranilic acid is used as the starting material, it is methylated to give methyl anthranilate.

From there on the process is the same as that used with phthalic anhydride.

The Maumee process yields a product with impurities that are, for the most part, different from those found in saccharin that has been manufactured by the RF process. The OTS impurity is not found in the Maumee-produced saccharin.

Subsequently, saccharin preparations that are manufactured from both processes are analyzed and may be further purified, but these purification steps are proprietory information.

Saccharin is generally prepared as the sodium salt although the calcium and ammonium salts are also available. The physical properties of saccharin and its salts are detailed in the Food Chemicals Codex (NAS, 1972).

The saccharin preparations that have been used in in-vivo studies were manufactured by the RF method, except in the 1977 study by the Canadian Health Protection Branch, which used saccharin that had been produced by the Maumee process (Canadian National Health and Welfare Ministry, 1977a,b). For the various in-vitro tests, lots of saccharin from both processes were used in addition to more highly purified samples.

Metabolism. In 1974, the NAS/NRC Subcommittee on Non-nutritive Sweeteners issued the report, Safety of Saccharin and Sodium Saccharin in the Human Diet (NAS, 1974). In addressing the questions of the carcinogenicity of saccharin in animals and the safety of saccharin in the human diet, the subcommittee devoted a good deal of attention to the metabolism of saccharin. The 1974 report, based on data from the intervening years, sub-

stantiated the conclusions of an earlier NAS report (NAS, 1970) that saccharin was readily absorbed and rapidly excreted, mostly in the urine, as unmetabolized saccharin.

The subcommittee covered three key areas in the physiologic disposition of saccharin--absorption, distribution and excretion, and metabolism. Its findings are summarized below.

Several studies have shown that most saccharin was rapidly absorbed during its passage from the stomach to the small intestine in the guinea pig, rat, mouse, dog, hamster, pig, and monkey, and that very little was found in the feces.

Saccharin was widely distributed throughout the body after ingestion but did not remain in tissues after a single dose. Multiple dosing in rats resulted in accumulation of saccharin in several tissues, especially in the bladder. However, saccharin was cleared rapidly after the dosing was discontinued. Saccharin was also shown to cross the placental wall in pregnant monkeys that had been given ^{14}C-saccharin by infusion. After the infusion, fetal blood levels exceeded maternal values and saccharin was cleared more slowly from fetal tissue than from maternal tissue.

In all species tested, saccharin was excreted primarily in the urine. Fecal excretion of saccharin varied from 3% to 40% in rats and averaged 3% in humans. Less than 7% of saccharin was excreted into bile; that larger amounts of fecal saccharin were likely due to incomplete absorption (Byard and Golberg, 1973; Lethco and Wallace, 1975; Minegishi et al., 1972).

Several studies demonstrated that the majority of orally administered ^{14}C-labelled saccharin was excreted unchanged in

the urine when given to guinea pigs, rats, mice, dogs, hamsters, and humans. In rats and monkeys, over 97% to 99% of the administered ^{14}C was accounted for as unchanged saccharin by 72 hours. Trace amounts (< 1% of the administered dose) of orthosulfamoylbenzoic acid and ammonium carboxybenzenesulfonate were detected in the urine of rats and monkeys in three studies. Saccharin was excreted virtually unchanged in humans.

Ball et al. (1977) reported a series of experiments, in which they investigated the fate of [3-^{14}C] saccharin in two men and one woman, in female rats, and in female rabbits. They fed 60 rats a diet containing 1% or 5% (w/v) saccharin for 3 to 12 months. This resulted in an average daily saccharin consumption of 0.2 g and 1 g, respectively. On the final day, 16 to 22 mg/kg of [3-^{14}C] saccharin was administered by gastric intubation. Twelve rats were given the oral dose of [3-^{14}C] saccharin with no pretreatment. Nine rabbits received a single dose of 6 mg/kg of [3-^{14}C] saccharin, and 18 rabbits received drinking water containing 1% saccharin (about 1.6 g/day) for 6 months before being given the dose of labelled saccharin.

Within 24 hours, about 95% of the dose of ^{14}C was eliminated from previously untreated rats, 76% in the urine and 14% in the feces. There was almost complete elimination of the ^{14}C dose by 6 days. The pattern was similar in the rats that had been pretreated with saccharin except that more ^{14}C was recovered in the feces. By 24 hours, 51% to 72% was recovered in the urine and 13% to 30% in the feces. In rabbits receiving no pretreatment with saccharin, there was almost complete recovery of ^{14}C by

48 hours; 82% was eliminated in the urine and 11% in the feces. Less saccharin was excreted in the feces of the pretreated rabbits. About 92% of the dose was excreted at 48 hours--83% in the urine and 4% in the feces. Analysis of the rat and rabbit urines by paper chromatography detected no metabolites of saccharin. The authors also found that the amount of $^{14}CO_2$ in the expired air of rats that had been pretreated with saccharin for 12 months was less than 0.03% of the dose of labelled saccharin.

The three human volunteers were given a single oral dose of 0.2 mg/kg of [3-^{14}C] saccharin and their urines and feces were analyzed for 4 days. These same subjects were then given three doses of saccharin totalling 1 g daily for 21 days. After the last dose, 0.2 mg/kg of labelled saccharin was administered. Saccharin was recovered almost entirely in the urine. At 24 hours, 85% to 92% of the ^{14}C dose was detected in the urine and less than 1.5% in the feces. By 4 days, there was almost complete recovery of the saccharin-labelled dose. There was 95% to 96% recovery in the urine and 3% to 5% in the feces. No metabolites of saccharin were detected in the urine.

In two additional experiments, livers and feces taken from previously unexposed rats and from rats kept on saccharin diets and feces taken from rats that were capable of metabolizing cyclamate to cyclohexylamine were incubated with ^{14}C saccharin. No compound other than saccharin was detected after the incubations.

From their data, Ball et al. (1977) concluded that, within the limits of the experimental methods, unchanged saccharin was

excreted by humans, rabbits, and rats and that chronic feeding of the sweetener did not produce further metabolism.

Couch et al. (1973) administered a 120 mg oral dose of sodium saccharin to a single subject. A blood sample was collected 5 minutes before the dose was given, and blood and urine were collected at 6, 12, and 24 hours. In a method developed by the authors, saccharin was identified as its N-methyl derivative by adding diazomethane to the tissue sample and using gas-liquid chromatography. By 6 hours, 43% of the dose was recovered in the urine and there was 96% recovery of unchanged saccharin by 24 hours. Analysis of the blood samples showed that the saccharin was bound to plasma proteins.

The mechanism of urinary excretion of saccharin in rats was investigated by Bourgoignie et al. (1977), who found that saccharin is excreted by a combination of filtration and tubular secretions in both sexes.

The ability of saccharin to bind to liver and bladder DNA was investigated by Lutz and Schlatter (1977). Two male rats weighing 173 and 180 g, were gavaged with ^{35}S-labelled saccharin and were killed 50 hours later. The total radioactivity administered to the rats was 4.57 and 4.53 μCi, corresponding to doses of 390 and 372 mg/kg, respectively. Urine and feces were collected at 0-24, 24-48, and 48-50 hours. DNA was isolated from the livers and bladders for radioactivity measurements.

By 24 hours, 66% and 84% of the two administered ^{35}S doses were recovered in the urine, and there was total recovery by 50 hours. Using thin-layer chromatography, the investigators found

that almost all of the radioactivity in the urine existed as unmetabolized saccharin. The yield of DNA from the bladder was small so that the samples from the two rats had to be pooled. A total of 0.68 mg of DNA was isolated from the bladder, while 2.75 and 3.33 mg were taken from the rat livers. Radioactivity measurements revealed that there was no incorporation of saccharin into the DNA. The limits of detection were 1×10^{-8} mol saccharin per mol DNA phosphate and 1×10^{-7} mol saccharin per mol DNA phosphate for the liver and bladder, respectively. Therefore, the authors concluded that it is unlikely that the carcinogenicity of saccharin is due to covalent binding to DNA but, rather, to secondary damage to the bladder epithelium.

In summary, the majority of data on the biotransformation of saccharin demonstrate that this compound is excreted unchanged predominantly in the urine in both humans and laboratory animals. There was generally a 90% to 99% recovery of the original dose in the urine; the remainder was detected in the feces. These levels varied somewhat depending on whether there was single or multiple dosing of saccharin. Up to 6% of a ^{14}C-labelled saccharin dose has been recovered in human feces. Generally, there has been less than 10% recovery in the feces of test animals, although up to 40% was recovered in the feces of some rats. Measurement of the expired air of rats given saccharin showed that less than 0.03% of the dose was detected as $^{14}CO_2$. Examination of urine and feces has shown that there are either no or very low levels of metabolites.

There are only three reports of saccharin biotransformation

products in the urine. Ammonium carboxybenzenesulfonate and orthosulfamoylbenzoic acid were detected in rats and monkeys but in amounts that were less than 1% of the administered dose. No evidence of saccharin biotransformation has been demonstrated in humans.

After repeated exposures, saccharin accumulates to some extent in organs such as the bladder, kidney, and liver, but particularly in the bladder wall. However, it is eliminated fairly rapidly after dosing is stopped. Whether single or multiple exposures are given, saccharin is almost completely eliminated within 24 to 72 hours.

Saccharin does not appear to bind covalently with DNA of the bladder or the liver.

Tumorigenesis--Bladder. Many chronic studies have been designed and conducted to determine the carcinogenicity of saccharin. All of them have been reviewed carefully by the committee.

In July 1970 an ad hoc subcommittee of the NAS Committee on Food Protection issued a report (NAS, 1970b) concluding that there was no evidence for the carcinogenicity of saccharin in the data that it reviewed. In 1974, the Subcommittee on Non-nutritive Sweeteners of the NAS Committee on Food Protectio reevaluated all available toxicity data on saccharin and concluded that, from the evidence of 11 chronic studies, saccharin could not be considered a carcinogen. That report (NAS, 1974) raised the possibility that OTS or other contaminants of saccharin that occur in large and variable concentrations might

be bladder carcinogens. Another issue raised by that report was the undefined and possibly confounding role of factors such as calculi and parasites, which are known to induce bladder tumors.

In 1977 an Advisory Panel of the Office of Technology Assessment reviewed all available information from chronic studies of saccharin (U.S. Congress, 1977). Its conclusion that saccharin was a bladder carcinogen in animals was based especially on the uniformly positive two-generation studies with rats.

In the present NAS evaluation, the committee reviewed 14 lifetime feeding studies to ascertain the chronic toxicity (including carcinogenicity) of saccharin. The experimental protocols can be divided into two categories: single-generation exposures (11 studies) and two-generation exposures (three studies). In the single-generation studies, animals were exposed orally, from weaning age through most or all of their lives, to doses ranging as high as 2,700 mg/kg/day (Table 3-1). The committee concludes that in the single-generation studies saccharin did not induce cancer in any organ.

Three two-generation studies were performed with saccharin (Table 3-2) (U.S. Dept. of Health, Education, and Welfare [USDHEW], 1973a,b; Canadian National Health and Welfare Ministry, 1977a,b; Wisconsin Alumni Research Foundation [WARF], 1973). In each study, rats of each sex of the parent generation (F_0) were fed saccharin in their diets from weaning through pregnancy and preweaning of their offspring. The F_1 generation was placed on the same diet as their parents for their entire lifespan. Thus, animals of the F_1 generation were

exposed to saccharin and its impurities as well as to their metabolites, transplacentally, via mothers' milk, and, subsequently, in their own diet. The following dose levels of saccharin were used in these studies: 0.01%, 0.1%, 1%, 5%, and 7.5% in the FDA study (USDHEW, 1973a); 0.05%, 0.5%, and 5% in the WARF study (Tisdel et al., 1974; WARF, 1973); and 5% in the Canadian study (Arnold et al., 1977b; Canadian National Health and Welfare Ministry, 1977). Extensive review of the pathological findings led to the results that are noted in Table 3-2. Bladder tumor incidence in treated males of all F_1 generations at the highest dose levels was consistently and statistically higher than that of controls. In addition, males of the F_0 generation in the Canadian study demonstrated significant incidence of bladder tumors at the 5% feeding level--an important and unique observation for the F_0 generation.

In summary, saccharin is a bladder carcinogen in male rats. The effects were observed consistently in the F_1 generation of two-generation studies. In only one of these three studies was saccharin a bladder carcinogen in the males of the F_0 generation.

Several investigators have studied the possibility that saccharin is a cocarcinogen or promoter. Their results have been equivocal. Hicks and coworkers have published a number of reports (Chowaniec et al., 1974; Hicks and Chowaniec, 1977; Hicks et al., 1973, 1975, 1977) in which saccharin was administered to rats in their drinking water at 2 g/kg/day or in their diet at 4 g/kg/day. A single initiating dose of N-methyl-N-nitrosourea (MNU) was instilled through a catheter into the urinary bladder when the rats were 6 to 8 weeks old. The animals were monitored

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TABLE 3-1

Results of One-Generation Saccharin Feeding Studies[a]

Study	Animals	Saccharin Mfg Process	Duration of Exp.	Dosage[b]	Number of Animals Start	Number of Animals Effective[c]
BioResearch Consultants, 1973	Rats (Charles-River)	RF[d]	27 mos.	1%, 5%	25/group	C 16 1% 13 5% 12
National Institute Hygienic Sciences, Japan, 1975	Rats (Wistar)	RF	28 mos.	2500 mg/kg	C 54 T 53	C 14 T 17
Litton Bionetics, 1973	Rats (Charles-River)	RF	26 mos.	1%, 5%	40-52/group	M F C 32 26 1% 38 29 5% 27 37
Schmahl, 1973	Rats (Sprague-Dawley)	RF	animal lifetime	0.2, 0.5%	52/group	M F C 52 52 0.2 52 52 0.5 52 52
Munro et al., 1973, 1975a	Rats (Charles-River Sprague-Dawley Derived)	RF	28 mos.	90, 270, 810, 2700 mg/kg	60/group	M F C 57 56 90 51 56 270 54 52 810 52 56 2700 54 54
Lessel, 1959	Rats (Boots)	RF	24 mos.	.005., .05, 0.5, 5.0%	20/group	M F C 6 9 .005 12 13 .05 8 10 0.5 9 9 5.0 3 2

							M	F
Hicks and Chowaniec, 1977; Hicks, personal communication	Rats (Wistar)	RF	28 mos.	g/kg	46-70/group	C	46	52
						T	70	68
							M	F
National Institute Hygienic Sciences, Japan, 1973	Mice	RF	21 mos.	0.2, 1.0, 5%	50/group	C	27	26
						T	23	22
						1.0	22	29
						5.0	19	28
							M	F
BioResearch Consultants, 1973	Mice (Charles-River CD-1)	RF	24 mos.	1%, 5%	20-36/group	C	19	17
						1%	14	14
							15	14
						5%	15	18
							19	18
							M	F
Althoff et al., 1975	Hamsters (Golden-Syrian)	RF	lifetime (80 wks)	.156, .312, .625, 1.25% (in drinking water)	30/group	C	18	15
						.156	13	13
						.312	17	16
						.625	24	17
						1.25	12	14
							M	F
Coulston et al., 1975	Monkey	RF	5-6 yrs.	20, 100, 500 mg/kg (in solution)	2-3/group	C	3	3
						20	2	2
						100	2	2
						500	3	3

[a] Negative = no significant difference between controls and treated.

[b] Either % of diet or mg/kg of body weight.

[c] Effective = number of animals that survived 80 weeks (rats) or longer on which bladder histopathology was done.

[d] RF = Remsen-Fahlberg Process.

TABLE 3-2

Results of Two-Generation Saccharin Feeding Studies

Study	Animals/ Generation	Saccharin Mfg. Process	Diet (Percentage of Diet)	Incidence of Bladder Cancer In Male Rats		Statistical Significance* (P)
				Control	Treated	
WARF, 1973	Sprague-Dawley F_1	Remsen-Fahlberg	5	0/14	8/14	.001
FDA (USDHEW, 1973a)	Sprague-Dawley F_1	Remsen-Fahlberg	5	1/25	1/21	N.S.
			7.5	1/25	7/23	.018
Canadian (Arnold, et al., 1977a)	Charles River (Sprague-Dawley Derived)/F_1	Maumee	5	0/42	12/45	.0002
	Charles River (Sprague-Dawley Derived)/ F_0	Maumee	5	1/36	7/38	.033

*Statistical Analysis was carried out according to the Fisher-Exact Test; P values were determined for one side of the curve indicating the probability value for an increase in tumor incidence.[4]

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for histologic and ultrastructural characteristics, premalignant changes, bladder calculi, and time to appearance of tumors. No bladder tumors were observed in control rats that received only MNU. The bladder tumor incidence with saccharin alone was less than 2%, but in combination with MNU the incidence rose to 52%. In rats given saccharin alone, tumors first appeared at 95 weeks; in rats given saccharin and MNU the tumors appeared at 9 weeks. Many of the saccharin-treated rats that developed tumors had bladder calculi; however, several animals had tumors but no bladder calculi. The parasite Trichosomoides crassicauda was not found in any of the rats.

Since several agents that had been tested in conjunction with MNU had been shown to produce tumors, there is the possibility that the development of tumors was due solely to MNU. Cyclophosphamide was given alone in 18 monthly i.p. injections or as a single i.p. injection given 2 weeks before or 2 weeks after MNU was administered. Although hyperplasia and hyperpolyploid cells developed in the bladder epithelium, no tumors resulted. However, the data for cyclophosphamide are not directly comparable to saccharin, since the latter was administered daily for prolonged periods.

The 1974 NAS report on saccharin contained evaluations of the early work of Hicks and colleagues. Its conclusions stated that "the deposition of exogenous materials in the urinary bladder is a highly artificial procedure. Furthermore, the question arises whether the saccharin or the bladder stones were cocarcinogenic in conjunction with MNU. [T]he role of impurities in the phenomenon...has not been resolved....[T]he observation [of co-

carcinogenesis] is complicated by the presence of a known bladder carcinogen, MNU. Considerably more research is needed to confirm and explain this finding."

Cohen et al. (1978) investigated the cocarcinogenicity of saccharin in rats using N-[4-(5-nitro-2-furyl)-2-thiazolyl]-formamide (FANFT). Male weanlings were given through their diet either 0.2% FANFT for 6 weeks followed by a control diet; 0.2% FANFT for 36 weeks followed by a control diet; 5% saccharin; 0.2% FANFT for 6 weeks then 5% saccharin; or 0.2% FANFT for 6 weeks, a control diet for 6 weeks, and then 5% saccharin. The experiment was continued for 2 years. The bladder cancer incidence rates were 16% and 100% for FANFT given for 6 and 36 weeks, 0% for saccharin alone, 89% for FANFT and saccharin, and 50% for FANFT plus saccharin given after a 6-week delay. These data suggest that saccharin promotes FANFT-initiated bladder cancer in rats.

Saccharin has also been administered to male and female rats in combination with another sweetener, cyclamate (Oser et al., 1975). Rats were fed a diet containing 0, 500, 1,120, or 2,500 mg/kg/day of a 10:1 cyclamate-saccharin mixture over 2 years. Bladder tumors were observed only at the highest dose. There were tumors in 12 of 70 rats, nine males, and three females. The 2,500 mg/kg dose is equivalent to about 5% of the diet. The tumor incidence that resulted was higher than that obtained with cyclamate or saccharin alone at comparable exposure levels in the one-generation feeding studies. This may suggest an additive or synergistic effect between the two sweeteners.

Bryan et al. (1970) and Bryan and Yoshida (1971) used a test system in which the cocarcinogenicity of saccharin was examined in connection with a cholesterol pellet. Twenty to 24 mg of a cholesterol pellet was implanted into the urinary bladders of a control group of 106 female mice (60 to 90 days old). The same amount of a cholesterol pellet containing 20% sodium saccharin was implanted in the bladders of 130 female mice. The animals were observed for up to 13 months. There was no difference in the average survival in days between the two groups. The incidence of urinary bladder carcinoma increased from about 12% in mice receiving only the cholesterol implantation to about 50% in mice given cholesterol and saccharin. Fifty percent of the saccharin was cleared from the pellet within 5.5 hours and 99% by 1.5 days. Of the more than 100 chemicals tested using the implantation method, saccharin was one of only 15 that induced bladder cancer in two or more trials.

Not all investigators have found saccharin to be a tumor-promoter or cocarcinogen. Roe et al. (1970) gave female mice (9 to 14 weeks old) a single dose of 0.2 ml polyethylene glycol (PEG) or 50 mg benzo[a]pyrene (BP) in PEG by intragastric instillation. After 7 days on a standard diet some mice received a diet containing 5% saccharin for up to 18 months while others were kept on a standard diet. There were 50 mice in each test group. No effect on survival rate was observed from any of the treatments. Mice that had been given only BP had increased numbers of hepatomas and of papillomas of the forestomach, compared to the control group that received only PEG. One mouse developed a carcinoma of the forestomach that was not seen in the control group. No benign

or malignant tumors of the forestomach were observed in the group receiving only saccharin; nor did saccharin given in combination with BP produce more tumors than those observed in the group that was given only BP. Bladder tumors were not observed from macroscopic examination, but the bladders were not examined microscopically. Roe et al. concluded that, under their test conditions, saccharin does not cause tumors in mice nor does it promote the tumor activity of BP.

Ershoff and Bajwa (1974) studied the effects of saccharin that was given in conjunction with 2-acetylaminofluorene (AAF). Female rats weighing 57 g were given 300 mg/kg of AAF alone or with 5% saccharin through their diet for 40 weeks. There were 12 rats in each experimental group and 12 rats in the control group. Animals were autopsied and their urinary bladders were examined microscopically. There was a 92% tumor incidence rate of mammary and ear duct tumors in rats given AAF for 40 weeks while the group given saccharin and AAF had only a 50% rate. The mucosal lining of urinary bladders in rats from both groups were hyperplastic and one rat given saccharin and AAF had precancerous changes of the epithelium. It was not clear why saccharin had this inhibitory effect on tumor induction, but the authors did not rule out the possibility that it may have been partly due to a decrease in the intake of calories and AAF in the saccharin-treated group.

Crampton is presently conducting studies on saccharin using the methods of Hicks and his colleagues (Chowaniec et al., 1974; Hicks and Chowaniec, 1977; Hicks et al.,

1973, 1975, 1977). Crampton's interim data have been presented in an FDA report that was prepared by Cranmer (1978). The rats were injected with MNU, then given 2% saccharin in their drinking water. Two different samples of saccharin were used. Only one sample contained the impurity OTS. The preliminary data have shown 12 bladder tumors (benign and malignant) in 51 rats administered only MNU; whereas, no tumors developed in this group in the experiments of Hicks and his colleagues. The tumor incidence did not increase in the groups of rats that received the saccharin samples in addition to MNU, which again differed from the observations by Hicks. These data indicate that saccharin does not promote bladder cancer when given through drinking water, but more extensive data from this experiment are needed before definitive conclusions can be drawn.

Studies using saccharin in combination with four different agents, MNU, FANFT, cyclamate, and cholesterol pellets, have shown saccharin to be a cocarcinogen or tumor promoter in the rat bladder. Negative results occurred in experiments with saccharin and BP in mice and saccharin and AAF in rats, but in these cases the initiating agent alone did not cause bladder tumors. Moreover, preliminary data by Crampton have not duplicated the promotion of bladder tumors that occurred in rats that were given saccharin and MNU (Cranmer, 1978). Cranmer (1978) reported a multiple agent study that is being conducted by Ito, who is testing saccharin in rats with either or both 4-(butylnitrosamino)-1-butanol (BBN) and caffeine. So far, there have been no data from Ito's studies to indicate whether saccharin is a promoter or a cocarcinogen.

Although the relevance of some of the methods used in these experiments, such as pellet implantation and direct bladder instillation of MNU, is questionable, the data in some of the experiments do indicate that saccharin can act as a promoter or cocarcinogen for bladder cancer. Since humans are rarely exposed to only a single agent, risk assessments for humans should consider the carcinogenic potential not only of saccharin alone but also of saccharin in combination with other agents.

Tumorigenesis--Other Organs. The committee has reviewed pathologic findings from organs other than the bladder. In four rat studies (USDHEW, 1973a,b; Canadian National Health and Welfare Ministry, 1977a,b; Munro et al, 1973; WARF, 1973) in which dietary levels of 5% or 7.5% saccharin were used and for which detailed pathology reports were available, there were more animals with lesions of the female reproductive tract in the saccharin-treated groups than in the control groups; however, the difference between the treated and control groups was not statistically significant.

The lesions that were found most frequently were benign uterine tumors and cystic ovaries. In the FDA study (USDHEW, 1973a,b), the Munro study (Munro et al., 1973, 1975; I. C. Munro, personal communication and unpublished data), and the Canadian F study (Canadian National Health and Welfare Ministry, 1977a,b; I. C. Munro, personal communication and unpublished data), there were increased numbers of animals with ovarian cysts; while in the WARF study (P. Dersc, personal communication; Tisdel et al., 1974; WARF, 1973), there was an increase in ovarian tumors. The

data are presented in Table 3-3.

The greatest differences between control and saccharin-treated animals were found in experimental situations in which the animals were mated. This suggests a possible hormonal involvement. However, no correlation was found between the reproductive-tract tumors and pituitary or adrenal lesions. Appropriate hormone assays were not performed.

In summary, as a result of detailed analyses of the pathology data, the committee concludes that the experimental evidence suggests that ingestion of saccharin at the 5% or 7.5% dietary level may have contributed to an increase in benign uterine tumors and ovarian lesions in female rats.

Tumorigenesis--Issues of Data Interpretation. Some aspects of the chronic toxicity/carcinogenicity studies warrant further elaboration because of possible misinterpretation. These issues are the determination of whether the doses tested met the criteria of "maximum tolerated dose"; the appropriateness of in-utero exposure in the testing protocol; the lack of dose-response for bladder cancer by saccharin; and the confounding of results by high sodium in the diet of treated animals or of the formation of calculi in the urine of saccharin-treated rats.

The doses of saccharin that produced bladder cancer in male rats were 5% and 7.5% of the diet. Examination of all the parameters that were measured revealed no significant adverse effect on survival or longevity other than those effects produced by carcinogenicity. In F_1 male weanlings

TABLE 3-3

Saccharin Ingestion[a] and Lesions of the Female Reproductive Tract in Rats
(Statistical Analysis)

	No. Animals with Ovarian Tumors			No. Animals with Cystic Ovaries			No. Animals with Uterine Tumors		
	C	T	P	C	T	P	C	T	P
Canadian F_0	0/48	0/49	—	10/48	11/49	.521	6/48	13/49	.068
Munro F_0	0/56	0/54	—	0/56	4/54	.055	2/56	4/54	.322
Canadian F_1	1/50	2/49	.492	4/50	12/49	.024	6/50	4/49	.833
WARF F_1	0/17	3/19	.136	—	—	—	1/17	3/19	.345
FDA F_1	0/16	0/22	—	2/16	6/22	.245	2/17	5/24	.374
Combined P_0[b]	—	—	—	—	—	.196	—	—	.041
Combined F_1	—	—	.115	—	—	.012	—	—	.438
Combined F_0 and F_1	—	—	.115	—	—	.010	—	—	.063

[a]All studies at 5% dietary level except the FDA study, which was at 7.5% level. C=Control, T=Treated, P=Statistical Significance.

[b]Statistical methods for combining data according to Cochran (1954) and Gart (1971) (one-sided, exact P values for an increased tumor incidence in treated animals).

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PAGE

in the three two-generation studies, treated animals had less weight gain than corresponding controls. However, the rate of growth of both treated and control rats after weaning was identical. The significance of the transient effect on body weight is unclear; however, it is possible that this effect reflects caloric restriction. In the Munro et al. (1973) study, an isocaloric regimen produced no difference in body weight during the weaning period. Differences in body weight--postpartum and through weaning--were observed in both sexes; whereas formation of bladder tumors occurred only in males. This suggested that the carcinogenic effect was not the result of the transient differences in body weight. To maximize the sensitivity of animal studies to detect carcinogenic activity--particularly weak activity--the highest tolerable dose that does not otherwise produce effects on longevity and survival must be used. Saccharin doses of 5% and 7.5% meet these criteria.

The studies in which saccharin produced bladder carcinoma employed the two-generation exposure design. This design was selected to mimic human exposure patterns which, for saccharin, often included ingestion by pregnant women with consequent exposure of the fetus in utero. Since the developing fetus often represents a highly susceptible stage to the toxic effects of agents, the determination of possible risks under such conditions of exposure appear reasonable for a substance widely dispersed in the food supply. The observation that saccharin crossed the placenta was additional incentive to

determine chronic toxicity from the time of conception. Five years ago, in-utero exposure/lifetime feeding designs were relatively new. Consequently, there had been no history from which safety could be evaluated.

Current review of saccharin studies using this design clearly indicate a consistent toxic response, both qualitatively and quantitatively, that leads convincingly to the conclusion that saccharin is a bladder carcinogen when exposure begins in the parental generation and occurs from the time of conception throughout life in the offspring. Whether briefer exposures yield similar risks has not been determined experimentally. The NAS study in 1974 concluded on the basis of two in-utero/lifetime exposure studies that commercial saccharin was a bladder carcinogen in laboratory animals but noted that the effect could not be ascribed to either saccharin or to one of its impurities (NAS, 1974).

Recent data strengthen the conclusion about the carcinogenic activity of saccharin per se. The results of the two-generation studies cannot be ascribed to toxicity during the reproductive process, since many reproductive studies as well as data on reproductive indexes from these studies have demonstrated no adverse reproductive effects. Thus, the committee concludes that the rationale for such a design is reasonable and that the implementation of the study did not generate confounding reproductive toxicity. The studies are considered valid for this risk assessment.

Animals exposed to sodium saccharin were also exposed to

high levels of sodium in their diets. Only the FDA study attempted to control for this element by exposing control animals to sodium carbonate; however, the judiciousness of testing with this anion has been questioned. The use of clearly matched controls would have been advisable for all studies. The possibility that high sodium intake affected the production of bladder cancer appears remote. On the one hand, cardiovascular disease (e.g., hypertension) would be expected from high sodium consumption, but histopathologic evaluations do not support such a conclusion. On the other hand, sodium could alter the disposition of saccharin, although the absence of biotransformation (even with repeated exposures) would argue against this. In addition, sodium, at least in the chloride form, does not appear to have carcinogenic properties. While the data are indirect, high sodium diets do not appear to confound the observation of bladder cancer from exposure to high doses of saccharin.

The possibility was raised that bladder cancer actually resulted from irritation of the bladder epithelium by foreign bodies such as calculi or parasites (NAS, 1974; and U.S. Congress, 1977). Such foreign bodies play an important role in the induction of bladder cancer. These factors cannot be ruled out entirely, although they were taken into limited account by these studies (USDHEW, 1973a,b; Canadian National Health and Welfare Ministry, 1977a,b; WARF, 1973). Gross calculi did not appear to be related to saccharin-induced bladder cancer; however, microcalculi have not been discounted. Bladder nematodes appear to have been ruled

out in the Canadian study (Canadian National Health and Welfare Ministry, 1977a,b) within the limitations of detection. Such non-specific effects due to calculi and parasites would not be expected to be sex-specific as was the incidence of bladder cancer. And the occurrence of parasites would be expected to afflict, with approximately equal frequency, both treated and control animals. Thus, these factors are not likely to be responsible for the observed bladder cancer.

Confidence in the biological significance of an adverse effect is greatly increased when the incidence of the lesion varies in proportion to dosage. Only two dose levels of saccharin (5% and 7.5%) have been associated with bladder cancer in male rats; however, no dose-response was evident. Nevertheless, such a phenomenon is compatible with a dose-response. The 5% feeding level may represent the beginning of the measurable dose-response for the number of experimental subjects employed in the study. At 1% saccharin in the diet, no increase in tumors was observed. A measurable effect might be detected at doses between 1% and 5% dietary levels; however, those doses have not been studied adequately. To increase the sensitivity of the carcinogen bioassay to detect bladder cancer at dietary levels of saccharin below 5%, the experimental design should be modified to expand the number of experimental animals.

An overall evaluation of the preceding issues leads the committee to conclude that the bladder carcinomas observed in the two-generation studies are related to saccharin exposure and are not confounded by the dose levels used, in-utero design,

lack of dose-response, or the possibility that sodium or foreign bodies significantly influenced the responses.

Noncarcinogenic Effects. In a 1974 report by the NAS/NRC Subcommittee on Nonnutritive Sweeteners (NAS, 1974), data on the reproductive and teratogenic effects of saccharin and sodium saccharin were reviewed and evaluated. The findings in this report are summarized below.

Reproductive Effects

Rats were fed saccharin in their diet at 0%, 0.5%, and 5% continuously through the growth, mating, gestation, and lactation stages. Mating occurred after the rats were on the saccharin diet for about 14 weeks and the offspring were observed for 28 days. There was no effect on mating efficiency, survival of the pups, or growth rate of the surviving offspring compared to controls. Saccharin-fed rats did have smaller average litter sizes and a lower average of live births than the controls, but these effects were not dose-related and were believed to be due to customary experimental variability.

In a six-generation study, mice were given sodium saccharin in their diets at 0.2% or 0.5%. There were some decreases in body weight at 21 days in some generations, but this was not a consistent finding. No consistent effects on fertility index, viability index, lactation index, and number of infertile males were observed over the six generations.

In a three-generation study in rats fed sodium saccharin at 0.01%, 0.1%, 1.0%, 5.0%, and 7.5%, the only reported effects were in the F_{1b} generation. There was an increase in preim-

plantation loss except at the 0.1% level and an increase in early deaths only at the 5% level. No effects were seen in the F_{2a}, F_{2b}, F_{3a}, and F_{3b} generations.

Teratogenic Effects

No evidence of teratogenicity was found in the reproductive studies described above.

In several studies reported during the 1960's, investigators found no teratogenic effects in mice, rats, and rabbits that were given saccharin.

Sodium saccharin that was injected into chick embryos at 0 and 96 hours of incubation caused growth retardation, poor survival to hatching, and minor beak defects. However, the subcommittee concluded that because these effects were commonly observed in chick embryo assay systems, their significance to safety evaluation was uncertain.

No effects on fetal survival, fetal weight, litter size, and fetal development were observed as a result of sodium saccharin that was given to rabbits at 0.6 g/kg/day on days 1 through 29 of pregnancy; to rabbits at 0.5 or 1.0 g/kg/day on days 8 through 16 of pregnancy; to rats at 6 g/kg/day on days 1 through 20 of pregnancy; and to rats at 0.5, 1.0, or 5.0 g/kg/day on days 8 through 16 of pregnancy.

No abnormalities were observed in the offspring of rats given sodium saccharin by stomach tube at 0.48-38 g/kg on days 7-13 of pregnancy and mice given sodium saccharin by stomach tube at 62.3-1,000 mg/kg on day 6 of pregnancy.

When saccharin and its sodium, calcium, or ammonium salts were administered to pregnant mice at up to 600 mg/kg for 10 consecutive days, there was no increase in teratogenic effects when compared to controls.

In summary, on the basis of the available data, the committee concludes that there is no evidence that saccharin or its salts produce teratogenic or reproductive effects in mammals.

Short-Term Tests for Genetic Effects. The Office of Technology Assessment (U.S. Congress, 1977) reviewed the existing literature on short-term tests on saccharin. It reported the results of 12 short-term tests conducted for OTA which tested samples of saccharin that were used in the recent positive carcinogenicity test in rats (Canadian National Health and Welfare Ministry, 1977a,b). Another review was recently completed by Kilbey et al. (1977).

The OTA panel concluded that although there are a number of positive studies in the literature, the results are equivocal. Of the 12 short-term tests conducted for OTA, three (sister chromatid exchange, mouse lymphoma L5178Y, and chromosome aberrations) were weakly positive, seven were negative, and two were in progress at the time of the panel's final report. Of the three positive tests, the sister chromatid exchange and mouse lymphoma results have been published as separate reports (Clive et al., 1978; Wolff and Rodin, 1978). Of the two incomplete studies, in-vitro transformation in mouse C3H 10T 1/2 is now complete (Mondal et al., 1978).

The in-vitro transformation studies and additional reports that have appeared in the literature since the OTA report are discussed

below. Other short-term tests have been described elsewhere (Kilbey et al., 1977; U.S. Congress, 1977).

In all but one of the short-term tests that have been reported since the OTA study, either negative or borderline positive results were observed. These studies neither convincingly confirm nor conflict with the weakly positive results reported in the OTA study. The exception is the study of Mondal et al. (1978), which demonstrated that highly purified saccharin is a promoter in the 10T 1/2 in-vitro transformation system. This study reported new data and expanded the list of short-term tests.

Test for Promoter Activity

In studies conducted for the OTA, Weinstein reported that saccharin was negative in a test for induction of plaminogen activator, which responds to the phorbol ester promoters (U.S. Congress, 1977).

Mondal et al. (1978), using the 10T 1/2 in-vitro transformation system, observed that highly purified saccharin can act as a weak promoting agent to cause significant in-vitro transformation if cells are treated with saccharin (100 µg/ml) in the presence of nontransforming doses (0.1 µg/ml) of the carcinogen and in-vitro transforming agent 3-methylcholanthrene. Saccharin itself is nontransforming, even at very high doses. The results of Mondal et al. are compelling in that the 10T 1/2 system is a well-established method for studying in-vitro transformation; all of the known promoting agents that have been tested (Mondal et al., 1978; C. Heidelberger, personal communication, 1978); the effect is not

borderline and is statistically significant; and the study appears to have been carefully and thoroughly conducted.

Chromosome Aberrations

In an abstract Masubuchi et al. (1978a) reported chromosome breaks and gaps in-vivo in mice after i.p. injection of 4 g/kg, a dose that was comparable to that received by rats in the Canadian positive carcinogenicity test (Canadian National Health and Welfare Ministry, 1977a,b) or in vitro in Chinese hamster cells (cell line not identified) after treatment with 10 to 30 mg/ml sodium saccharin (purity not specified). Three papers in Japanese (Masubuchi et al., 1977a,b; Yoshida et al., 1977) from the same research group were not evaluated. In another abstract, Ochi and Tonomura (1978) report similar results in human fibroblast cultures (from aborted fetuses) after treatment with 1-10 mg/ml saccharin.

These results support those of Hsie and coworkers, which are described in the OTA report (U.S. Congress, 1977); however, there are enough uncertainties so that these data cannot be regarded as confirmation of the preliminary data of Hsie and colleagues. The data presented in the abstracts are not sufficiently complete to permit a definitive analysis. These studies report only breaks and gaps which are less certain indicators of mutagenic potential than other chromosome aberrations, such as those found by Hsie and colleagues, and can occur as a result of nonspecific toxicity. Also, the doses used were in the range in which saccharin is known to be toxic to Chinese hamster cells, thus suggesting that data on protocol, toxicity, and actual numbers of aberrations observed be

made available before these studies can be regarded as supportive of the preliminary data from Hsie's group which appear in the OTA report.

Dominant Lethal Test (DLT) in Mice

As noted in the OTA report (U.S. Congress, 1977) the dominant lethal data on saccharin are equivocal with both positive (Šram and Zudova, 1974) and negative results (Machemer and Lorke, 1975a, b). Šram and Zudova and Masubuchi et al. (1978a,b) reported saccharin as positive in the dominant lethal test (DLT). A rigorous appraisal of Masubuchi's work is not possible without an English translation of the study. However, very few animals were used in the study, and the statistical procedure used in analyzing the data (the Chi-square test) does not test for variance about the mean and is inappropriate for use with dominant lethal data (Haseman and Soares, 1976).

The experimental design and statistical analyses of Šram and Zudova (1974) appear adequate; however, the results that they obtained in the DLT and the chromosomal test are confusing, i.e., the dominant lethal effect that they observed appears to have resulted primarily from preimplantation loss (Šram and Zudova, 1974). The data of Burkii and Sheridan (1978) indicate that early deaths such as these are usually the result of large amounts of chromosomal damage. The chromosomal effects that were observed by Šram and Zudova were not of the magnitude that would be expected to produce a dominant lethal effect consisting solely of preimplantation death. In light of Burkii and Sheridan's work and the chromosomal effects observed by Šram and Zudova, one would have expected to see (if,

in fact, saccharin caused the dominant lethal effect) an increase in postimplantation deaths as well as preimplantation deaths.

Salmonella (Ames) Test

The OTA report described negative studies by Stoltz et al. (1977) on highly purified samples of saccharin that were used in the positive Canadian carcinogenicity test. These studies were confirmed by Yamasaki et al. (1977). Recently, Ashby et al. (1978) have further confirmed this finding.

Batzinger et al. (1977) slightly modified the Salmonella test (Ames et al., 1975) and reported weakly positive mutagenic activity in impure samples of saccharin and in urine from mice that had consumed several samples of either highly pure or impure saccharin. They have also submitted to the committee, in the form of several tables, some additional data on extracts of urine from treated mice. Some of these results are suggestive, but a definitive judgment, especially on the highly pure samples of saccharin, is difficult. Results from testing urine from saccharin-treated mice: (1) From results reported by Batzinger et al. on urine from saccharin-treated mice, an estimate of the actual data obtained (information in the paper does not permit an exact calculation) indicates that the number of revertants observed were less than twice the spontaneous revertant background for all of the samples, except for one sample (presumably impure) that was obtained from a local pharmacy. For this sample, results were very weak, but were obtained consistently (E. Bueding, personal communication, 1978). With the highly purified saccharin, the number of revertants, over a background of 158, must have been less than 10 -- a result that is not statistically significant.

Compared to the substantially negative data that were obtained using urine of mice that had been treated with highly purified saccharin samples, these data suggest that there are mutagenic impurities present in impure commercial samples of saccharin. (2) A supplementary table that was submitted to the committee presents mutagenicity data that were obtained by testing extracts of urine from mice that had been treated with highly purified saccharin. Large volumes (up to 30 ml) of urine were extracted (solvent unknown). The results are still barely two times the spontaneous background rate. Although these results are suggestive for extensive data with appropriate statistical analyses, the results of control experiments are needed to analyze this work adequately.

Results testing impure and pure saccharin directly: Batzinger et al. (1977) reported results that are negative for the purified saccharin samples (confirming previous work cited in the OTA report) and that are weakly positive with an apparent dose-response effect for two commercial (presumably impure) samples. These results are suggestive but require confirmation. In unpublished experiments using the modified assay of Batzinger et al., Maron and McCann (U.S. Congress, 1977) and Simmon (personal communication, 1978) were unable to reproduce the results of Batzinger et al. on commercial samples that were most likely equivalent to those used by Batzinger and colleagues.

DNA Repair

Stich, in studies conducted for the OTA report (U.S. Congress, 1977), found saccharin negative in tests for unscheduled DNA synthesis. Recently, Ochi and Tonomura (1978) measured unscheduled DNA synthesis (by silver grain counts over non-S cells) in cultured

saccharin-exposed, human cells after treatment with 1, 5, or 10 mg/ml. These results give some indication of a weak, dose-related increase in counts. However, in their abstract (the complete manuscript was not available) they do not discuss the statistical procedures used in analyzing their data nor do they give any information regarding within-group variation. Since the reported differences between groups are very small, i.e., control: 1.3 grains versus 1.7, 2.1, and 3.5 for 1, 5, and 10 mg saccharin/ml, respectively, these data must be viewed cautiously. Variation among cells within these groups could easily result in a lack of statistical significance. Additional information is necessary before this result could be considered positive.

Drosophila Sex-Linked Recessive Lethal Test

McCann has discussed the results of sex-linked recessive lethal tests conducted by Valencia (1978) in which Drosophila were exposed to saccharin in their diet. The results of these tests were essentially negative.

More recently, Kramers (1977) tested two samples of saccharin (both produced by Sherwin-Williams and identified as P & B and S1022, respectively) and two contaminants of saccharin, ortho-toluenesulfonamide and paratoluenesulfonamide. Compounds were either fed or injected. The results indicated that the P & B saccharin (produced by the Maumee process) was weakly mutagenic and that the observed effect was consistent and reproducible. Neither of the two contaminants nor the S1022 saccharin (also Maumee) were positive, confirming Valencia and Abrahamsen's earlier negative results on S1022 (U.S. Congress, 1977). In light of these data, Kramers concludes

that saccharin is marginally mutagenic in Drosophila and that the two tested contaminants are not mutagenic.

Experimental Findings--Impurities of Saccharin

Chemistry. Impurities have been identified in commercial saccharin preparations made from both the Remsen-Fahlberg (RF) and the Maumee (M) processes. Over 30 substances have been reported from one source or another to be impurities in saccharin (Figures 3-3, 3-4, and 3-5) (Arters, 1978; Compton, personal communication, 1978), although not all have been well characterized or quantified. The methods for producing saccharin are constantly being refined so that the nature and concentration of impurities continually vary, but in the general direction of a more pure saccharin preparation. Even the concentration of impurities in saccharin preparations from the same manufacturer vary from lot to lot. In general, the level of impurities has been greater in saccharin that has been produced by the RF process than by the M process. RF saccharin may have up to 7,000 ppm of impurities. One M saccharin sample had 3,000 ppm of impurities, although the amount in M saccharin is usually very much lower.

The laboratories of the Canadian Health Protection Branch (Stavric and Klassen, 1975, 1977; Stavric et al., 1974, 1976, 1977, 1978; Stoltz et al., 1977) and Battelle (Arters, 1978; Compton, personal communication, 1978; Kinzer, personal communication, 1978; Zienty, personal communication, 1978) have done the most extensive work in isolating and identifying the impurities in commercial saccharin. A total of 14 impurities has been quanti-

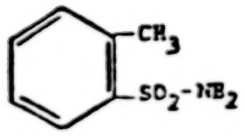
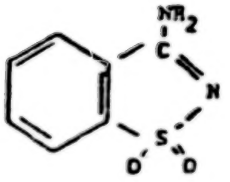
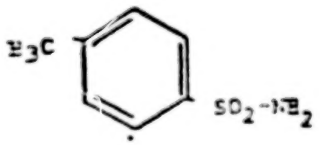
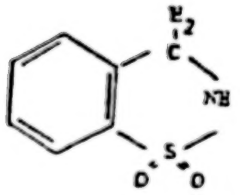
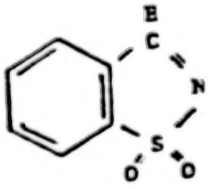
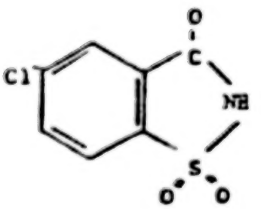
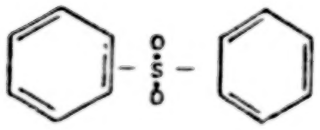
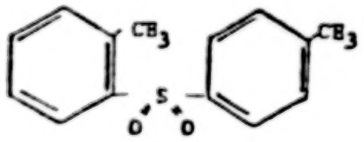
	Approximate Amount Present		Approximate Amount Present
	4-5 yrs. ago or earlier up to 6000 ppm. Recent preparations up to 25 ppm (or lower)		1 ppm
O-toluenesulfonamide		3-aminobenzisothiazol-s-dioxide	
	up to 5 ppm		10 ppm
p-toluenesulfonamide		1,2-benzisothiazoline-1, 1-dioxide	
	10 ppm		not quantitative (about 2-3 ppm)
1,2-benzisothiazole 1, 1-dioxide		5-chlorosaccharin	

FIGURE 3-3. Impurities in saccharin manufactured by the Remsen-Fahlberg Process.

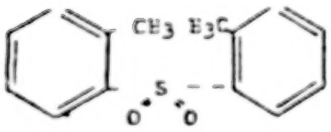
Approximate Amount Present: Total amount of all diphenylsulfones under 5 ppm (1 sample ▶50 ppm).



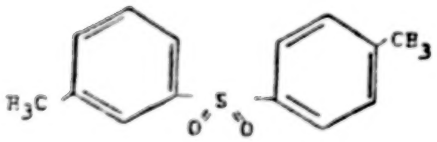
diphenylsulfone



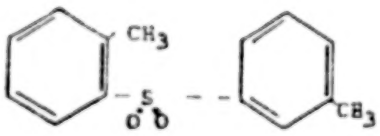
o,p-ditolylsulfone



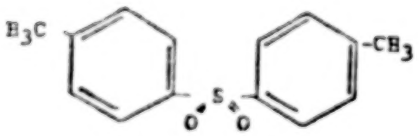
o,o'-ditolylsulfone



m,p-ditolylsulfone

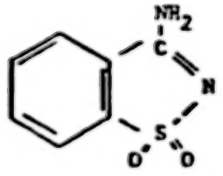


o,m-ditolylsulfone

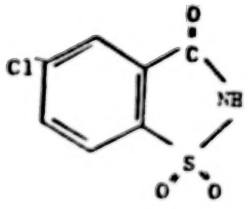


p,p-ditolylsulfone

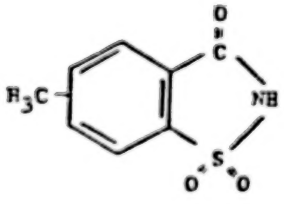
FIGURE 3-3 (cont'd)



3-aminobenzisothiazol-s-dioxide (M, RF)

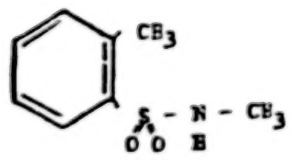


5-chlorosaccharin (M, RF)

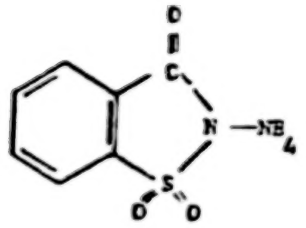


methyl saccharin (M)

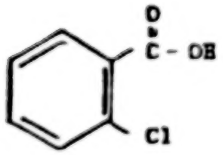
FIGURE 3-4. Impurities in saccharin manufactured by the Maumee Process. Organic solvent extract impurities total 10-30 ppm. Total water-soluble extract impurities not yet determined.



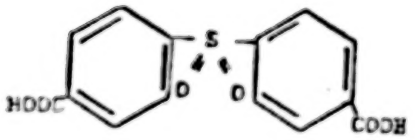
N-methyl o-toluenesulfonamide (RF)



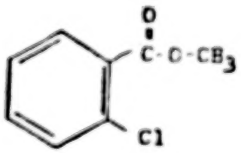
ammonium saccharin (M)



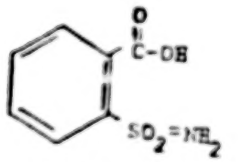
o-chlorobenzoic acid (RF)



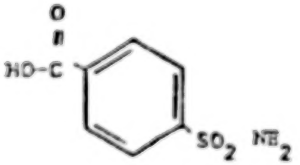
4,4'-dibenzoylsulfone (RF)



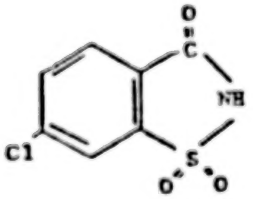
methyl o-chlorobenzoate (RF)



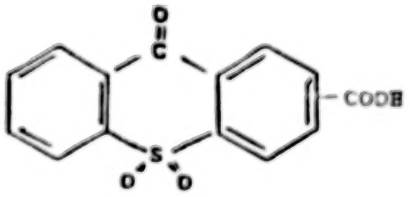
o-sulfamoylbenzoic acid (M,RF)



p-sulfamoylbenzoic acid (RF)

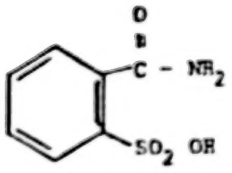


6-chlorosaccharin (RF)

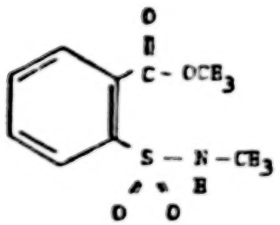


2 or 3 carboxy thiaxanthone-5-dioxide (RF)

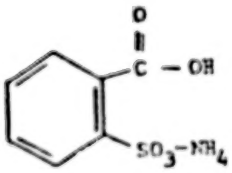
FIGURE 3-5. Impurities identified but concentrations are not known.



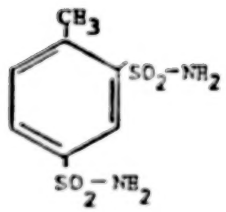
o-sulfobenzamide (RF)



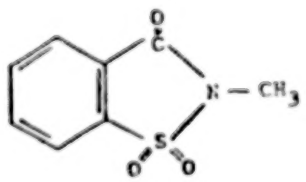
methyl-N-methylsulfamoyl-benzoate (RF)



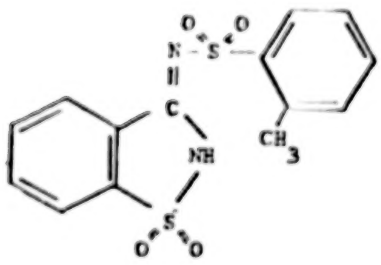
o-sulfobenzoic acid, ammonium salt (M, RF)



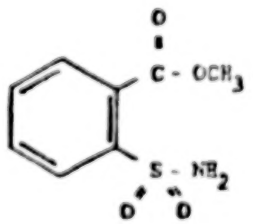
2,4-toluenedisulfonamide (RF)



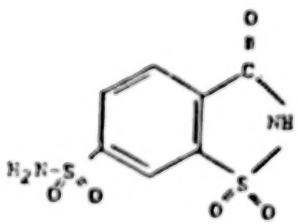
N-methyl saccharin (M)



saccharin-o-toluenesulfonylimide (RF)



methyl-o-sulfamoyl-benzoate (RF)



saccharin-6-sulfonamide (RF)

FIGURE 3-5. (cont'd)

fied to date. These are orthotoluenesulfonamide (OTS), p-toluenesulfonamide (PTS), 1,2-benzisothiazole-1,1-dioxide, 1,2-benzisothiazoline-1,1-dioxide (BIT), diphenylsulfone, o,o'-, o,m'-, o,p'-, m,p'-, and p,p'-ditolylsulfone, n-tetracosane, 4-chlorosaccharin (CS), methylsaccharin, and aminobenzisothiazole-1,1-dioxide (aBIT). Also lead, selenium, silver, arsenic, bismuth cadmium, copper, mercury, and tin were below Food Chemical Codex (NAS, 1972) specifications (Calorie Control Council, 1978). Most of this analytical work has been done using gas-liquid chromatography and high pressure liquid chromatography. Authentic samples have been used, primarily to establish retention times. These substances have been confirmed using mass spectrometry, thin-layer chromatography, and ultraviolet (UV), infrared (IR), and nuclear magnetic resonance spectroscopy.

OTS is the major impurity found in RF saccharin. Stavric and coworkers at the Canadian Health Protection Branch have found concentrations of OTS in saccharin preparations that ranged from 2.5 to 5,050 ppm. OTS was not detected in saccharin that was prepared by the Maumee process (limit of detection, 0.1 ppm). Battelle Laboratories, Inc. has analyzed several saccharin samples that were produced by the two methods. RF saccharin contained OTS mainly in concentrations of from 200 to 400 ppm, although concentrations were as high as 5,650 ppm, PTS from <1 to 210 ppm, and BIT from 1 to 10 ppm. M-derived saccharin had concentrations of OTS and PTS that were less than 1 ppm, aBIT from 4 to 48 ppm, an unidentified substance thought to be an isomer of aBIT from 0 to 306 ppm, and CS from <100 to 2,600

ppm in one sample (limit of detection, 100 ppm). In addition to the above-mentioned compounds, Stavric has isolated and quantified organic solvent soluble impurities ranging from 5 to 20 ppm for M saccharin and 51 to 305 ppm for RF saccharin. Only this fraction has been shown to be mutagenic in short-term tests; however, fractions from different lots of saccharin have not been consistently mutagenic (Stavric et al., 1977; Stavric, personal communication, 1978; Stoltz et al., 1977). The levels of identified organic soluble impurities bear no relationship to their ability to produce in-vitro mutagenesis. Table 3-4 shows this lack of correlation. From these data there is no reason to believe that this fraction is an important indicator of the overall toxicity of saccharin. For example, the saccharin that produced bladder cancer in the FDA tests has an organic extract without mutagenic activity. Methyl saccharin, the major impurity from Maumee saccharin lot S-1022, has no demonstrable mutagenic activity (Stavric et al., 1977).

The level of impurities in saccharin is important because an impurity, not saccharin, could have been responsible for the bladder cancer observed in rats. For example, OTS is found in RF saccharin in much larger quantities than any other impurity. The 1974 NAS report estimated that in the FDA and WARF studies, which showed bladder cancers in rats, the animals were receiving OTS in concentrations ranging from 20 to 368 ppm (7.5% dietary level of saccharin) and from 12.5 to 18.0 ppm (5% dietary level), respectively. On the other hand, the 1977 Canadian study used M-processed saccharin that contained no OTS, but bladder cancers developed. On the basis of the analytical data, which indicate

TABLE 3-4

Comparison of Organic Impurities and Mutagenicity[a]

Samples[b]	Organic Impurities, ppm	Mutagenicity
S 1022	13	+
GS 1233	5	-
6368	13	+
S 1469	20	+
GSC 0129	16	+
QA 80	86	-
QB 125	305	-
191010	51	+

[a] From Stavric et al., 1977.

[b] The first four samples are from the Maumee process; the others, from the RF process.

that relatively low concentrations of impurities other than OTS are present in saccharin, if observed bladder cancers were due to a contaminant, that compound would have to be a very potent bladder carcinogen.

Metabolism. Of the over 30 impurities that have been identified in commercial saccharin, less than half have been well quantified, and there are toxicity and metabolic data on only a handful. In a series of experiments (Ball et al., 1978; Renwick, 1978; Renwick et al., 1978; Renwick and Williams, 1978), the investigators administered the following saccharin impurities by stomach tube to adult female rats: [Me-^{14}C]toluene-2-sulfonamide (OTS), [3-^{14}C]benz[d]isothiazoline-1,1-dioxide (BIT), 3-amino[3-^{14}C]benz[d]isothiazoline-1,1-dioxide (aBIT), 5-chlorosaccharin (CS), [Me-^{14}C]toluene-4-sulfonamide (PTS), and 4-sulfamoyl[carboxy-^{14}C] benzoic acid (SBA). Urine and feces samples were taken daily for up to 7 days. Urinary metabolites were separated by thin-layer and paper chromatography and confirmed using gas-liquid chromatography and mass spectrometry. The doses, percent recovery of ^{14}C, and biotransformation products are shown in Table 3-5. There were three rats at each of the dose levels.

The rate at which all saccharin impurities were eliminated by the rats was similar. At the lowest doses about 90% to 95% of the ^{14}C was recovered within 24 hours.

Similar results were obtained for humans receiving OTS and BIT. Their metabolic patterns are shown on Table 3-6.

The authors concluded that, if large amounts of saccharin do

TABLE 3-5

Metabolic Fate of Saccharin Impurities Administered to Rats[a]

Compound	Dose	Time	% of Dose Excreted			Urinary Metabolites	% of Dose Excreted
			Urine	Feces	Total		
PTS	29 mg/kg	1d	78	4	95	PTS	2
		5d	81	6	101	4-sulfamoyl-benzyl alcohol	3-5
						4-sulfamoyl-benzaldehyde	2
						4-sulfamoyl-benzoic acid	94-96
	200 mg/kg	1d	63	1	78	N-acetyltoluene-4-sulfonamide	2
		4d	70	4	90	No 4-sulfamoyl-benzaldehyde, otherwise same as at lower dose	
SBA	22 mg/kg	1d	74	16	94	SBA	98-102
		6d	77	25	105		
aBIT	25 mg/kg	1d	87	2	91	aBIT	99
		4d	89	2	95	Unidentified metabolite	1
CS	80 mg/kg	1d	76	2	82	CS	90
		4d	81	4	88	5-chloro-2-sulfamoyl-benzoic acid	traces
BIT	40 mg/kg	1d	92	2	97	2-sulfamoyl benzoic acid	35
		7d	94	3	101	2-sulfamoyl benzyl alcohol	15
	400 mg/kg	1d	50	5	60	saccharin	30
		6d	74	12	92	BIT	5-10
						Labile precursor of BIT	20
OTS	20 mg/kg	1d	78	4	92	OTS	6
		7d	88	5	104	2-sulfamoyl-benzoic acid	2
	120 mg/kg	1d	58	4	70	2-sulfamoyl-benzyl alcohol:	
		3d	72	6	87	unconjugated	37
	200 mg/kg	1d	36	4	43	glucoronic acid	23
		7d	75	7	90	sulfate	17
						saccharin	3
						N-acetyltoluene-2-sulfonamide	6

[a]From Ball et al., 1978: Renwick, 1978; Renwick et al., 1978; Renwick and Williams, 1978.

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TABLE 3-6

Metabolic Fate of Two Saccharin Impurities Administered to Humans

Compound	Sex of Subject	mg/subject	Time	Percent of Dose Excreted			Urinary Metabolites	% of Dose Excreted
				Urine	Feces	Total		
BIT[a]	M	37	1d	90	trace	90	saccharin	50
			2d	92	trace	92	2-sulfanomyl benzoic acid	7
			4d	93	trace	93	unconjugated 2-sulfamoyl-benzyl alcohol	8
							conjugated 2-sulfamoyl benzyl alcohol	40
OTS[b]	M	14	1d	63	trace	63	unconjugated and conjugated 2-sulfamoylbenzyl alcohol	43
			2d	91	trace	92	saccharin	40
			4d	100	trace	100	2-sulfamoylbenzoic acid	4
	M	30	1d	43	c	c	N-acetyltoluene-2-sulfonamide	2
			2d	72	c	c	OTS	3
			4d	88	c	c		
	F	14	1d	48	trace	48		
			2d	80	trace	80		
			4d	97	trace	98		

[a]Data from Renwick and Williams, 1978.

[b]Data from Renwick et al., 1978.

[c]Not determined.

not interfere with renal elimination or biotransformation, saccharin impurities would not accumulate in animals receiving saccharin-containing diets. Because OTS and BIT are not found in Maumee process saccharin, the only current manufacturing method in the United States, the metabolism of these impurities is of academic interest only.

Chronic Toxicity. OTS is the only impurity found in commercial saccharin for which possible chronic effects have been investigated. Arnold et al. (1977a) of the Canadian Health Protection Branch conducted long-term toxicity tests in rats. They attempted to determine whether previously observed increases in bladder cancer were possibly due to OTS, the major impurity found in RF saccharin. In the Canadian study, there were 50 male and 50 female rats in each of the following dietary groups: control; OTS at 2.5, 25, and 250 mg/kg/day; OTS at 250 mg/kg/day with 1% ammonium chloride (NH_4Cl) in the drinking water; and 5% OTS-free sodium saccharin. The feeding study began when the rats were 32 days old. The F_0 rats were bred at 100 days. Fifty pups of each sex from each group were randomly selected and given the parental diets for their lifetimes. In this manner, the F_1 rats were exposed from the time of conception, through the nursing period, and then for the remainder of their lives. The doses of OTS were equivalent to the amounts ingested by the rats in the WARF and FDA studies, in which saccharin-containing OTS was used. Ammonium chloride was added to the drinking water of one group to prevent alkaline urine, which has been associated with the

production of bladder calculi and bladder tumors in mice.

Rats were examined daily for general health status and for any signs of toxicity. Investigators maintained complete records of weight, food consumption, and histopathologic analysis at necropsy. Effects on reproduction were measured by recording fertility index, gestation index, viability index, lactation index, and average litter size.

The general health status of all rats was found to be good. F_0 females and F_0 and F_1 males, which received 250 mg/kg/day of OTS with or without ammonium chloride, had significantly lower body-weight gain than controls, while saccharin-treated rats had a moderately lower growth rate during the weaning period than controls. There were no significant differences in mean time until death between treated rats and controls. A total of 10 bladder and kidney stones were observed in the rats: one in a control rat and the rest in animals that had been exposed to saccharin and OTS. Arnold and his colleagues observed that the incidence of stones did not appear to be related to treatment.

Effects on reproduction from exposure to saccharin or OTS were minimal. There were differences in the viability and lactation indices between controls and rats given OTS at 2.5 mg/kg/day. Rats given OTS at 250 mg/kg/day plus ammonium chloride also had a smaller viability index, and there was a decrease in average litter size in the group given OTS at 250 mg/kg/day. Despite some of these differences, the authors concluded that there were no treatment-related effects on reproduction.

Malignant bladder tumors were detected only in the saccharin-

treated rats: three in F_0 males, eight in F_1 males, and two in F_1 females. In addition, there were three malignant lesions of the kidney pelvis: two in F_0 females and one in an F_0 male. There was one urethral carcinoma in an F_1 male. The difference in tumor incidence between F_0 and F_1 males and controls was statistically significant. In contrast OTS exposure produced no malignant bladder tumors.

Benign bladder tumors were observed, including one each in an F_0 male and female at the lowest dose of OTS, two in F_1 females at the lowest dose, and one in an F_0 male at the highest dose. One F_0 male control developed a benign bladder tumor, and there were nine benign urinary tract tumors (eight bladder tumors) in saccharin-treated male rats.

Schmahl (1978) also investigated the carcinogenic potential of OTS that was given to rats in their diets. Three-month-old rats were given 0, 20, or 200 mg/kg/day of OTS over their lifetime. Initially, there were 38 females and 38 male rats in each group.

Weight gain and behavior were normal in all rats throughout the experiment. OTS had no effect on lifespan in comparison to controls. A large number of animals in all three test groups developed lymphosarcomas of unexplained etiology. One animal in the high-dose group developed bladder cancer after 759 days. In addition, four rats at the high-dose and three rats at the low-dose had bladder papillomas. The sex of these rats was not identified. No bladder tumors were found in the control group. There were eight leukemias in OTS-treated rats compared with

controls; however, the incidence was not dose-related. There were five leukemias in the low-dose group and three in the high-dose group. It could not be determined whether or not the leukemias were related to OTS exposure.

The data from the Canadian study demonstrate that OTS-free saccharin is capable of producing bladder cancer in rats and that, under the conditions of the study, OTS is not a urinary bladder carcinogen in rats. However, Schmahl, using similar doses of OTS, observed some bladder tumors in rats. He suggested that OTS may be a carcinogen of low potency. Considering both of these studies, it is highly improbable that OTS alone, if at all, would have been responsible for the bladder cancers that were observed in the FDA and WARF studies. Another impurity could have been responsible for the bladder tumors but only if it was a very potent carcinogen because only small concentrations of impurities other than OTS have been found in saccharin.

Short-Term Tests for Genetic Effects. The studies by Stoltz et al. (U.S. Congress, 1977) demonstrated that chloroform extracts containing impurities in one lot of Maumee saccharin that was used in the recent positive rat carcinogenicity test were weakly mutagenic in the Salmonella test. More recent, substantially negative, results from tests of organic extracts (solvent and extraction procedures unknown) of lot S1022, (as well as extracts of another sample reported positive by Stavric et al. (1977) were conducted by Litton Bionetics (1977) on samples supplied by Sherwin-Williams. These negative results do not clearly contradict the earlier positive finding because

most of the doses tested were smaller than those that gave positive results in the tests by Stavric et al. In preliminary results of a study conducted for the Calorie Control Council, Battelle Laboratories, Inc. confirmed the positive findings of Stavric et al. (Riggin et al., 1978). Following up their earlier work, Stavric, Stoltz, and their colleagues are attempting to isolate and identify the impurities that are mutagenic.

In the study conducted by Battelle Laboratories, Inc. (see above), about 50% by weight of the impurities extracted from Lot S1469 (a sample that Stavric et al. extracted and found to be weakly mutagenic) were chemically identified and some of these, along with additional chemicals previously identified as impurities in Maumee saccharin, were tested for mutagenicity in TA98 in the Salmonella test. Only a few of the identified impurities were tested. The 17 impurities tested were negative, with the exception of the thiazoline and thiazole compound, which are toxic at the high doses used. Since one of these (3-amino-benzisothiazol-1,1-dioxide), has been predicted to be mutagenic (see below), lower nontoxic doses should be tested.

Structure Activity Correlations. Since many of the impurities of saccharin had not been tested individually for their toxicity, particularly for carcinogenesis and mutagenesis, a structure-activity analysis was undertaken to determine the likelihood that these impurities might be mutagenic when tested in Salmonella systems. Twelve impurities were evaluated with the Genesee Toxicity Estimation Survey (K. Enslein, personal communication, 1978).

The results indicated that only 5-chlorosaccharin and 3-aminobenzisothiazol-1,1-dioxide may be weakly mutagenic. The other compounds evaluated are predicted to be nonmutagenic in the Ames assay. Since such structure-activity correlation is found only in the early stages of development, the predicted outcome must be verified experimentally before conclusions can be drawn; however, such a system can be applied to the setting of priorities for testing.

Risk Estimates

A chemical that has been associated with an increased cancer incidence in bioassays of laboratory animals is likely to be a carcinogen in humans. Extrapolation to humans of cancer incidence in animals is necessary to quantify the expected degree of risk for humans that are exposed to concentrations of the chemical that differ from those in the bioassays of animals. This extrapolation procedure consists of two basic steps:

1. within the test animal species, extrapolation of the experimental results of tests performed at high exposure or dose levels to much lower exposures in animals, which correspond to human exposures; and
2. extrapolation of these estimated risks for animals at low doses to the risks for humans at comparable levels.

The first step in this process requires the assumption of some biological model, which implies a mathematical rule that relates the dose level of a particular carcinogen to an ob-

servable response, e.g., the occurrence of a particular type of tumor at any time within the animal's natural lifespan or lifetime for the duration of the study. This assumption is normally required since the animal studies are conducted at much higher exposure levels than are commonly found for human exposures. These high exposure levels must be used to obtain measurable results with a limited number of animals. At dose levels that correspond to common human exposures, several thousand animals would be needed to estimate the increased carcinogenic risk in humans.

Many theoretical dose-response models of carcinogenesis have been proposed, each of which leads to a particular mathematical form for this dose-response relationship. All theories have one concept in common: that there is no known uniform threshold dose below which any carcinogenic response is impossible for all individuals at risk. Even if thresholds do actually exist, it is scientifically impossible to measure them or to prove their existence. In addition, the assumption of one uniform threshold for heterogenous groups is unrealistic. It is much more likely that each member of the population has an individual threshold level which is some complex function of unique biochemical and physiological composition. A further argument against use of threshold models for the estimation of attributable risk is that the environment contains many carcinogenic agents and that the particular chemical in question may be acting additively over and above this "background." Therefore, since tumors do appear spontaneously in a control population, the threshold, assuming it does exist, has probably already been exceeded by the environmental background. Craig

and Miller (1974), in a review of 151 dose-response curves, found only one to be inconsistent with the no-threshold hypothesis.

Some of the more commonly used mathematical extrapolation modes are the following:

The probit model is derived from the assumption that each member of the population has his own tolerance level for the chemical, below which there will be no response and above which the subject will respond. These tolerances are further assumed to vary among members of the population and to follow a log-normal probability distribution. Mantel and Bryan (1961) have suggested use of a modification of this model for extrapolation of carcinogenesis bioassays from high to low doses. Since the tolerance distribution for the homogenous laboratory animal population should have a smaller variation than that of the heterogenous human population, they suggest that the risk extrapolation be based on a model with a more shallow slope than that observed in the bioassay. This shallow slope should be no greater than the average true slope over the extrapolation range. A slope of one probit per 10-fold change in dose is commonly used for this Mantel-Bryan extrapolation.

The single-hit, or single-event, model is derived from the assumption that cancer starts in a single cell as the result of some random event, or "hit", which produces an irreversible change in the cell's DNA. It is further assumed that the probability of this event, attributable to the carcinogen in question, is proportional to the exposure level.

The multi-stage model (Crump et al., 1976), a generalization

of the single-event model, is derived by assuming that the carcinogenic process consists of some unknown number of stages that are required for cancer expression. The probability of at least one of the transitions from one stage to another is assumed to be a property of the particular carcinogen in the same manner as the single-event model.

Other models, such as the log-logistic and multi-hit models (Food Safety Council, 1978) have also been proposed, but the three models described above produce a range of extrapolations that would be obtained by most other models. Models of dose-response based on the actions and reactions on in-vivo chemical and physiologic processes have also been proposed (Gehring and Blau, 1977). These are determined by a series of differential equations corresponding to multicompartmental models of the chemical processes within the body that correspond to the internal fate of the chemical carcinogen.

The difficulty with using any of these dose-response models for high- to low-dose extrapolation purposes is their similarity over the observable response range, 5% to 95% response rates, contrasted with their dissimilarity in the range of very low response rates (Table 3-7).

Although all three models are similar in the observation range, the lower part of the table shows that extrapolation to exposure levels that are expected to give very low response rates is highly dependent upon the choice of mathematical model. The upper part of Table 3-7 shows that three of the most commonly used models differ by very little over a 256-fold dose range. At a dose that is 1/1000 of the 50% response

TABLE 3-7

Expected Response Rates as a Function of Dose for Different Dose-Response Models[a]

Relative Dose	Log Normal,%	Log Logistic,%	Single Hit,%
16	98	96	99+
8	93	92	99
4	84	84	94
2	69	70	75
1	50	50	50
.50	31	30	29
.25	16	16	16
.125	7	8	8
.063	2	4	4
0.01	.05	.4	.7
0.001	.00035	.026	.07
0.0001	.0000001	.0016	.007

[a] Data from USDHEW, 1971.

dose, the single-hit model gives an estimated response rate that is 200 times as large as the log-normal model. The fact that a limited animal bioassay that is conducted at dose levels high enough to give observable response rates cannot discriminate among these various models and the fact that these same models are substantially divergent at lower dose levels provides the major uncertainty for high- to low-dose extrapolation.

When using a model that is fit to the experimental result and is then used for extrapolation, it is assumed that the dose-response relationship observed at these high-dose levels will continue to hold throughout the entire spectrum of exposure levels. This assumption has been questioned by toxicologists and other health scientists. The effective exposure level, the amount of the carcinogen actually reaching the target cells and molecules, may well be some complex function of the absorption, distribution, biotransformation, and excretion of the host. Each factor may depend upon and influence the level of the carcinogen to which the animals are exposed. The in-vivo mechanisms that relate environmental chemical exposure levels to the levels that reach the target cells cannot be adequately quantified; thus, proportionality between the environmental exposure level and the effective exposure level is commonly assumed. This assumption is no doubt an oversimplification of the true relationship; however, without information on metabolic pathways, activation and deactivation systems, and other pharmacokinetic considerations, it is generally accepted.

The second step in the human risk assessment process is

extrapolation from laboratory animals to humans. For compounds that are known carcinogens in animal models as well as in humans, significant differences can be observed both among species and among various strains within species. Some animals are hypersensitive while others are refractory to the effect of the same chemical carcinogen. In some cases, differences in site specificity can be observed among various strains and species. Many of these differences can be related to metabolic factors, i.e., the compounds are metabolized through pathways that generate an ultimate toxicant or carcinogen. This metabolic activity is focused in specific organs, thereby increasing the probability of a toxic response within that organ. Within the framework of metabolism, the rates of biotransformation are also quite critical. The relative rates of activation and inactivation are important factors in determining the duration of exposure of target molecules to the carcinogenic substance. Systemic distribution may play a vital role, since the ultimate toxicant may be generated in one organ and redistributed to another to exert its toxic effects. Repair mechanisms and their rates also affect the ultimate manifestations of the lesions. If the rate of repair is relatively fast, one can expect that far more agent is necessary to produce irreversible biochemical lesions that lead to clinical manifestations. Conversely, when rates of repair are slow, relatively small quantities of an agent may be required to elicit a toxic syndrome such as cancer. Routes of excretion and rates of elimination are also vital in removing the toxicant or carcinogen from the locus in which it can combine with the

target receptors.

The National Academy of Sciences (1975) has recommended that carcinogenicity testing be conducted in more than one species and that the results obtained with the most sensitive species be applied to human populations. Adjustments for "equivalent exposure levels" between animals and humans must be made. This conversion process should depend upon the routes of exposure, possibly different, for the animals and humans, information on comparative metabolism of the chemical compound, and information on the similarities and dissimilarities of all relevant biochemical and physiological parameters of the two species. When this type of information is unknown, a simple proposed conversion rule can be used. This rule is based on the assumption that the locus of action for any chemical is on some, perhaps unknown, receptor. It further assumes that different mammalian species exhibit essential similarities except for size. Accordingly, it follows that any appropriate surface area in an organism will be approximately proportional to the 2/3 power of its weight (USDHEW, 1976). This "surface area rule" can be mathematically stated for any two species as:

$$\frac{\text{dose}_1 \ (\text{mg/day})}{\text{dose}_2 \ (\text{mg/day})} = \frac{w_1^{2/3} \ (\text{mg})}{w_2^{2/3} \ (\text{mg})}$$

If it is also assumed that the food or air requirements for different species are dependent upon surface areas, then conversion between species is direct when exposure is given in

terms of concentrations in the food or drink (Mantel and Schneiderman, 1975). An additional conversion rule is obtained from standard toxicological methodology (USDHEW, 1959), which equates dose levels on a milligram of dose per kilogram of body weight basis. These rules apply when the exposure levels are given as dose per unit of time, i.e., "dose rates". When human exposure is constant, or nearly so, over an entire lifetime, the results of chronic, constant exposure in lifetime experiments with animals may be directly extrapolated without any corrections for length of exposure. An approach based on total lifetime exposure per unit of body weight has also been used to equate species-to-species exposure levels (NAS, 1974). In a recent comparison of experimental results in animals and epidemiologic results in humans, these species-to-species extrapolation methods proved to be uniformly better than any other (NAS, 1974).

The variability involved in extrapolation between rats and humans based on these "equivalent dose" rules is shown in the following examples:

- Direct equivalence between species when dose is expressed as a percent of the daily diet. This implicitly assumes that continuous exposures over the lifetimes of two species are equivalent and not dependent upon the lifetime lengths. Human exposure to one 12-oz can of diet soft drink (10 mg of saccharin/oz is equivalent to 0.12 g of saccharin ingested per day). Assuming that an adult consumes 1,825 g/day, this represents

0.007% of the daily diet.

- Dose equivalence between two animal species when dose, expressed in absolute amounts, is proportional to the 2/3 power of their weights. This is the "surface area" rule, which also assumes that continuous exposure over a lifetime is not dependent upon the lifetime length. This dose-equivalence calculation is based on the assumption that human weight is 70 kg, rat weight is 400 g, and a rat's daily food consumption is 20 g. Therefore, a human daily consumption of 0.12 g/day is equivalent to a rat's daily consumption of 0.00384 g/day [=0.12/(70/0.4)2/3], which represents 0.02% of a rat's daily diet.
- Dose equivalence when dose is expressed in terms of daily amount ingested per unit of body weight. Using the previous assumptions, a human daily ingestion of 0.12 g/day equals 1.714 mg/kg/day, which for a rat represents 0.0034% of its daily diet.
- Dose equivalence when dose is expressed in terms of total lifetime ingestion per unit of body weight. Assuming 60 years of exposure to one diet drink for a 70 kg man, total ingestion is 37.5 g/kg/lifetime. Assuming a 400-g rat eating 20 g/day for 2 years, this would be the equivalent of a daily saccharin ingestion of 0.1% in his diet.

These dose-equivalence rules result in estimates of a rat

dose, in terms of percentage of dietary intake, corresponding to a human intake of 0.12 g/day, that range from 0.0034% to 0.1%, a 30-fold difference.

Table 3-8 presents a number of extrapolations that have been made to estimate the yearly cancer incidence in humans, each of whom has an assumed life expectancy of 70 years and a daily consumption of one 12-oz can of diet soft drink per day throughout life. In all of the extrapolations, calculations are based on data from the two-generation rat bioassays (USDHEW, 1973a,b; Canadian National Health and Welfare Minist., 1977a,b; WARF, 1973).

Table 3-8 clearly demonstrates that both the selected method of dose adjustment between species as well as the method of extrapolating from high to low doses determine the estimate of human risk. This table shows the extremely wide variability inherent in this risk-extrapolation process. There is no basis, at present, for determining which of these figures, if any, accurately reflect human risk from saccharin consumption.

Evaluation: Summary and Conclusions

Based on the evaluation of the data from laboratory investigations of saccharin, the committee has reached the following conclusions about the toxicity and potential human risks from exposure to saccharin.

1. Little biotransformation of saccharin has been detected in laboratory animals and none has been observed in humans. Because of the limits of experimental detection, it is possible that a small percentage of saccharin may be modified enzymatically.

TABLE 3-8

Estimated Human Risks from Saccharin Ingestion of 0.12 g/day

Rat dose adjusted to human dose by surface area rule	Lifetime cases/ million exposed	Cases per 50 million/yr.
Method of high- to low-dose extrapolation		
Single-hit model (Hoel, 1977)	1,200	840
Multi-stage model (with quadratic term) (Hoel, 1977)	5	3.5
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	450	315
Rat dose adjusted to human dose by mg/kg/day equivalence		
Single-hit model (Saccharin and Its Salts, 1977)	210	147
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	21	14.7
Rat dose adjusted to human dose by mg/kg/lifetime equivalence		
Method of high- to low-dose extrapolations		
Single-hit model (Brown, 1977)	5,200	3,640
Multi-hit model (Scientific Committee of the Food Safety Council, 1978)	.001	0.0007
Mantel-Bryan probit model (Brown, 1978)	4,200	2,940

Saccharin is rapidly absorbed via the gastrointestinal tract, is distributed widely throughout the body, crosses the placental wall, and is eliminated mainly in the urine. Accumulations of saccharin in several tissues including the bladder have been demonstrated following repeated exposures. The committee concludes that either saccharin is unusual in that its carcinogenic effects are due to the unmetabolized parent compound or the effects are due to small quantities of undetected metabolites. The accumulation of saccharin in the bladder epithelium may play a role in the formation of bladder cancer.

2. When tested in two-generation studies, saccharin is a bladder carcinogen for male rats. A significant increase in bladder cancer was found consistently in male offspring exposed continuously in utero and throughout life. In one two-generation study, a significant increase in bladder cancer occurred in males of the parental generation.

Studies using saccharin in combination with some chemical carcinogens have shown that saccharin promotes tumor development in the bladder of rats. Since humans are exposed to a variety of chemical carcinogens in their environment, the carcinogenic risk from saccharin as a promoter may be considerably greater than that indicated by the single compound studies. Because the process of cancer promotion is little understood, the estimation of risks to humans from these experimental data are not feasible at present.

The committee concludes that the following factors in design of the two-generation chronic studies did not confound the interpretation of the results: the doses studied (maximum tolerated dose), in-utero exposure, high sodium content of diet in treated versus control animals, and the possibility of microcalculi in

the urinary bladder of treated versus control animals.

Since animal studies that are properly conducted to detect carcinogenic activity are qualitatively predictive of human responses, the committee concludes that saccharin ingestion presents a predicted cancer risk to humans. However, because of the substantial uncertainties in extrapolating from experimental doses to human exposure levels, the committee concludes that quantitation of risks to humans cannot be made with confidence (Table 3-8).

3. An increase in benign uterine tumors and ovarian lesions in saccharin-treated rats was suggested in a few studies.

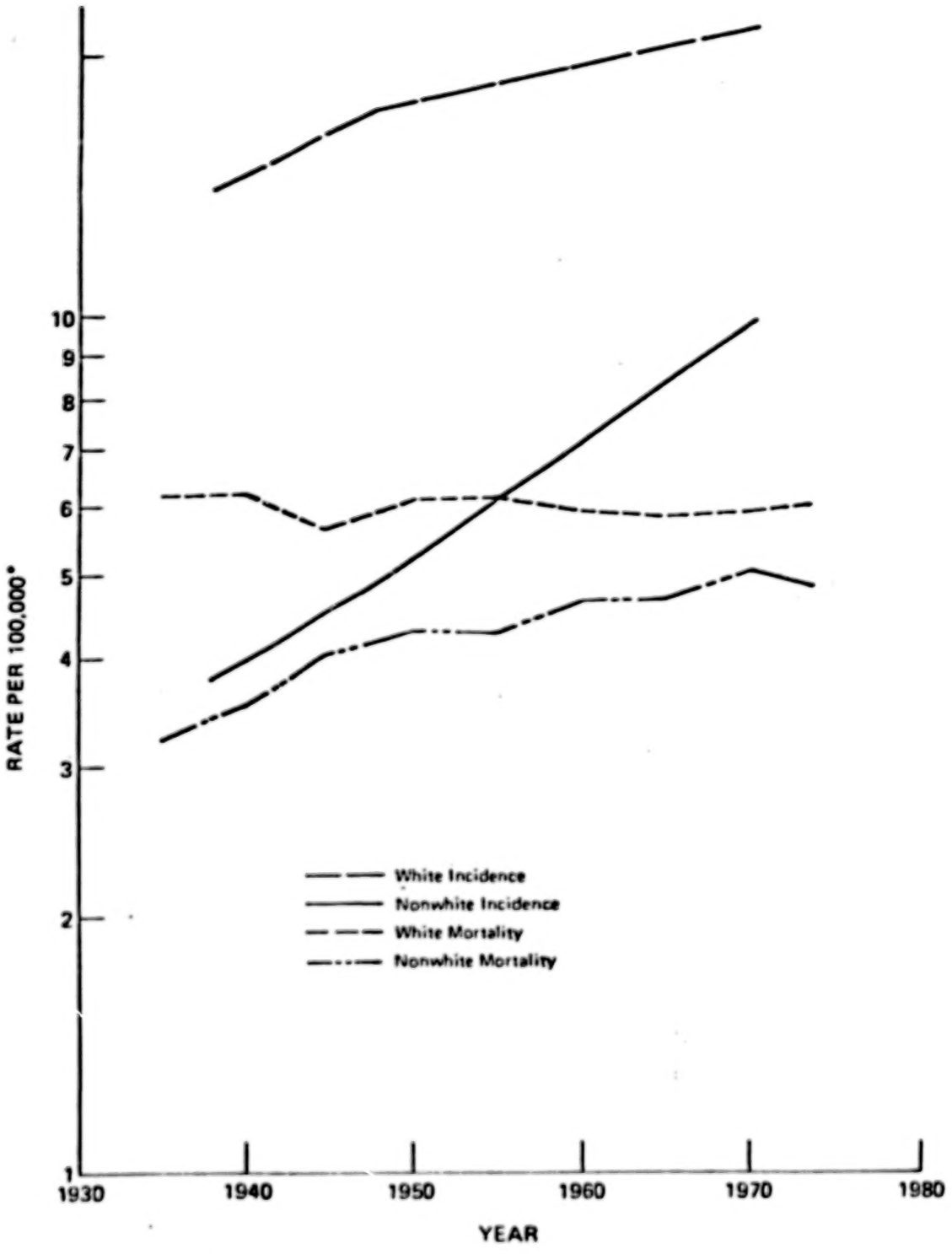
4. Orthotoluenesulfonamide, the major impurity of RF saccharin, is not carcinogenic in rats in a study that is properly designed to detect carcinogenesis. The possibility that other minor impurities of saccharin are responsible for carcinogenic activity of commercial saccharin cannot be eliminated. However, the committee believes that the probability of occurrence is extremely remote for the following reasons: a) RF saccharin used in the FDA and WARF studies had different patterns of impurities, yet produced the same carcinogenic responses (i.e., bladder cancer in males); b) the very much purer Maumee process saccharin has also produced bladder cancer in males; c) in Maumee saccharin the impurities are each present in such low concentrations that if they were carcinogenic, they would be required to be of exquisite potency.

5. Short-term tests for genetic effects have been conducted with saccharin and some of its impurities. Results of 16 assays were negative, while those of five (including a promotion assay)

were positive. Because these assays evaluate varying types of genetic effects and because saccharin appears to be a carcinogen of low potency, the variation in findings might be expected. The committee concludes that these studies are compatible with the in-vivo carcinogenic effects; however, the results do not provide definitive information on the interpretation of risks to humans.

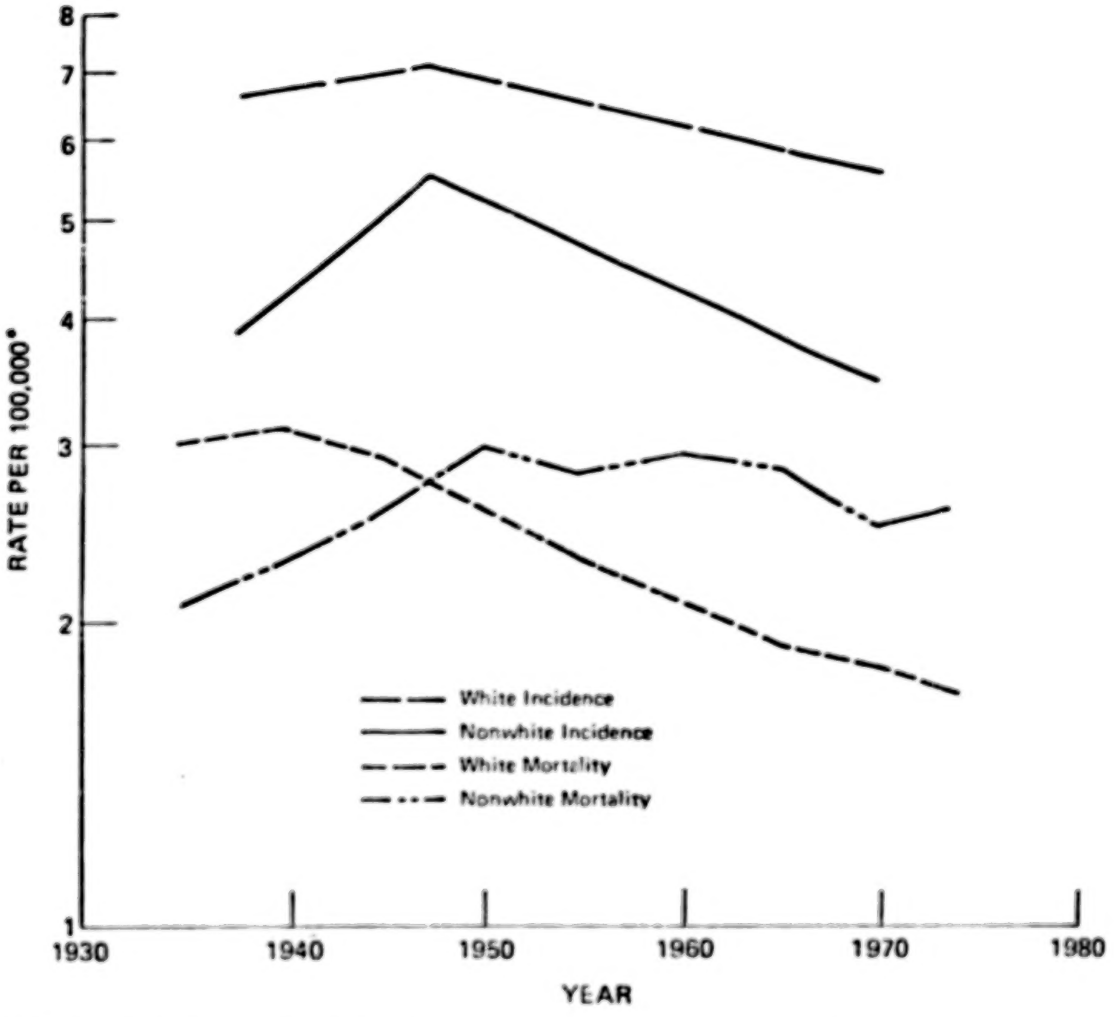
HUMAN POPULATION STUDIES

There are about 30,000 new cases of bladder cancer per year in the United States (American Cancer Society, 1978) and about 10,000 deaths per year where bladder cancer is the underlying cause (USDHEW, 1978). Approximately 75% of the cases occur among males. Figure 3-6 shows that the incidence is rising slowly for all males; however, the mortality rates are increasing only for nonwhite males (Devesa and Silverman, 1978). On the other hand, both incidence and mortality are generally declining for all females (Figure 3-7). Tables 3-9 and 3-10 show the age-specific mortality rates and the age-adjusted rates for all four race-sex groups (Mason et al., 1975, 1976). Previous descriptive epidemiologic research has shown that there is an increased frequency of lower urinary tract tumors in whites, males, Jews, urban residents, and people in the middle class (Cole, 1975). Bladder cancer incidence is known to be elevated in places where the population is exposed to the parasite Schistosoma haematobium (Cole, 1975). The most important risk indicators for this disease in the United States are smoking (Wynder and Goldsmith, 1977) and occupation (Cole, 1975), especially exposure to benzidine and β-napthylamine in the dyestuffs and rubber industries. Cole (1975) estimated that smoking



*Age adjusted to the 1950 U.S. population.

FIGURE 3-6. Male incidence and mortality rates for bladder cancer by race. Data from Devesa and Silverman, 1978.



*Age adjusted to the 1950 U.S. population.

FIGURE 3-7. Female incidence and mortality rates for bladder cancer by race. Data from Devesa and Silverman, 1978.

TABLE 3-9

Age-Specific Bladder Cancer Mortality Rates (Per 100,000)
U.S. Whites, 1950-1969[a]

Age	Males	Females
0-4	0.08	0.03
5-9	0.02	0.01
10-14	0.01	0.00
15-19	0.01	0.00
20-24	0.01	0.00
25-29	0.02	0.03
30-34	0.09	0.07
35-39	0.24	0.20
40-44	0.77	0.42
45-49	2.05	0.91
50-54	4.88	1.68
55-59	10.17	3.09
60-64	19.20	5.49
70-74	48.70	16.34
75-84	78.14	30.92
85+	111.49	50.54
TOTAL U.S. (age-adjusted)	6.78	2.39

[a] From Mason et al., 1975.

TABLE 3-10

Age-Specific Bladder Cancer Mortality Rates (Per 100,000)
U.S. Nonwhites, 1950-1969[a]

Age	Males	Females
0-4	0.05	0.02
5-9	0.01	0.02
10-14	0.00	0.00
15-19	0.01	0.01
20-24	0.04	0.01
25-29	0.09	0.05
30-34	0.18	0.21
35-39	0.67	0.64
40-44	1.59	1.42
45-49	3.60	2.78
50-54	8.36	5.86
55-59	12.26	8.11
60-64	19.60	10.76
65-69	24.55	13.95
70-74	32.61	17.21
75-85	36.10	21.38
85+	39.12	22.71
TOTAL U.S. (age-adjusted)	5.05	3.05

[a] From Mason et al., 1976.

accounts for 39% of the bladder cancer in males and 29% in females. Hazardous occupations account for 18% and 6% of bladder cancer in males and females, respectively. An unknown component accounts for 43% of the male and 65% of the female bladder cancer (Cole, 1975). Much of this unexplained component may be associated with coffee drinking (Cole, 1975; Morgan and Jain, 1974; Simon et al., 1975).

Three types of epidemiologic studies are reported in this chapter: time-trend studies, prospective studies, and retrospective case-control studies. All three studies were designed to determine whether there is a higher probability (or risk) of bladder cancer with exposure to saccharin than in its absence. The methods and results of these studies illustrate the difficulties that are encountered with epidemiologic data.

First, many of the studies were originally conducted for purposes that are unrelated to the present goal of determining the association, if any, of saccharin use with bladder cancer or other health effects. These studies rarely have detailed information on saccharin consumption because their purpose was to investigate other factors associated with bladder cancer such as cigarette smoking or coffee drinking.

Second, investigations of this relationship are designed to detect a strong association if it exists, but they may include too few study subjects to measure a weak one. Since the number of persons using saccharin is so great, even weak associations are important in predicting risks to health.

Finally, with the most competent design and with adequate numbers of subjects to identify weak associations, an investigator will often be unable to distinguish the expected association from the confounding effect of some other factor. Such variables can be excluded by appropriate study design when the factors are known in advance. Since unknown factors

cannot be formally excluded, it is ultimately a matter of judgment whether an association that persists after ruling out all known confounding factors should be accepted as causal. If the persisting association is strong, e.g., a tenfold or greater increase in a disease risk, it is difficult to defend the position that an unsuspected factor may be responsible. However, if the persisting association is weak, e.g., less than a twofold increase, such an unsuspected variable may indeed be responsible. Cigarette smoking or hazardous occupations may be variables that confound low-level associations between saccharin use and the occurrence of bladder cancer. Ultimately, a weak association may be demonstrated by intervention studies, clinical trials, or prophylactic trials. There have been no intervention studies of saccharin. Consequently, the interpretation of any results must be judgmental at present.

Epidemiologic Studies--Time Trend Analyses

Time-trend studies provide crude measurements that relate disease rates with other characteristics of population groups. Generally, these studies cannot indicate direct associations of disease rates with a carcinogen if the substance is not strongly carcinogenic (i.e., the disease risk is low) or if only a short time has elapsed from exposure to observation. Two time-trend studies measured the change in bladder cancer mortality rates against the use of saccharin (and cyclamates)--one in England (Armstrong and Doll, 1974) and one in the United States (Burbank and Fraumeni, 1970). Because of extensive saccharin use beginning during World War II in England, Armstrong and Doll (1974) investigated the possibility of a concomitant increase in the bladder cancer death rate. However, they found no evidence of an increase in bladder cancer mortality

that could be attributed to the greater use of saccharin. Although there was an increase in the rate of bladder cancer (greater in males than in females), an assumed contribution by saccharin could not be separated from the increase that was attributed to cigarette smoking.

In the United States, Burbank and Fraumeni (1970) examined bladder cancer death rates from 1950 to 1967 to determine if there was any correlation with the dramatic increase in the consumption of a 10:1 cyclamate-saccharin mixture which began in 1962. They did not find an association of sweetener consumption with the change in the rate of bladder cancer mortality, but did note that the dose might have been too low and that the observation period might have been insufficient for them to detect any effect. This is logical given that the latent period of bladder cancer is estimated to be from 18 to 45 years (Cole, 1975).

Studies of Diabetics and Cancer

Diabetics are heavy users of saccharin and other artificial sweeteners. Armstrong et al. (1976) reported that 66.6% of the male and 55.2% of the female members of the British Diabetic Association used saccharin tablets. This was determined from a 10% random sample of the membership (3,096 replies received from 4,000 members--77.4% response rate). Males consumed an average of 5.9 tablets per day; females, 3.4.[1] Of three studies in which the risk of bladder cancer among diabetics was investigated (Armstrong and Doll, 1975; Armstrong et al., 1976; Kessler, 1970), none has shown an excess.

From death certificates obtained from the Registrar-General for

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[1] Assuming the average tablet size to be a half grain (containing 26.4 mg of saccharin), this amounts to an average of 156 mg of saccharin per day in tablet form for males (2.2 mg/kg body weight) and 90 mg/day for females (1.5 mg/kg body weight).

England and Wales, Armstrong and Doll (1975) determined the frequency with which diabetes was mentioned on 18,733 certificates of death from bladder cancer and 19,709 certificates that cited other cancers, excluding cancer of the lung and pancreas. The study covered the period between January 1, 1966 and December 31, 1972. They hypothesized that there would be a greater frequency of diabetes mentioned among bladder cancer deaths than among other cancers because diabetics used a larger amount of saccharin. They reported the relative frequency to be 0.98, which did not differ significantly from 1, the null value.

Armstrong et al. (1976) assessed the risk of death from bladder cancer in a prospective study of 5,971 members of the British Diabetic Association. Individuals were studied from 5 to 8 years during the follow-up period from 1965 to 1973. The expected numbers of deaths were calculated by applying rates that were derived from a 10% random sample of all deaths occurring in England and Wales in 1972 to the age- and sex-specific person-years of observation. There were four observed and 5.8 expected cases of bladder cancer, which resulted in a standardized mortality ratio (SMR) of 70. This did not differ significantly from 100.

Kessler (1970) reported the cancer mortality profile of 21,447 white diabetics who were diagnosed at the Joslin Clinic from January 1930 to July 1956. The clinic records were used to identify all cancer deaths occurring before January 1, 1960, the date on which the study terminated. The expected number of cancer deaths was obtained by applying the Massachusetts age- and sex-specific rates to the person-years of observation from 1931 to 1959. For males 18.1 deaths from bladder cancer were expected and 14 occurred; for females, 11.5 deaths were expected and seven occurred. The SMR was 77 for males and 61 for females, neither of

which differed significantly from 100 (the null value).

The need to identify a group known to be high users of saccharin has led epidemiologists to focus on diabetics (Armstrong and Doll, 1975; Armstrong et al., 1976; Kessler, 1970). This approach has produced no evidence to demonstrate an association between bladder cancer and dietary habits of diabetics. In general, diabetics are not particularly useful in epidemiologic studies of cancer incidence and mortality. Any result from studies of cancer of diabetics is difficult to generalize to the non-diabetic population because of several attributes of their disease state and their behavior. For example, diabetics, as a group, smoke less (Armstrong and Doll, 1975; Christiansen, 1978); many of them observe therapeutic diets; bladder function is often abnormal in diabetics; and diabetics differ metabolically and genetically from the general population. In addition, they appear to seek medical care more often than the average individual. These studies of diabetics, like the time-trend studies, are investigations of group rather than individual characteristics and do not include information on the levels of saccharin consumption or the smoking habits of individual diabetics.

Case-Control Studies: Artificial Sweeteners and Bladder Cancer

There have been six case-control studies in which the consumption of saccharin among bladder cancer cases was compared with that of a group without bladder cancer. Two studies measured saccharin use by mail questionnaire and four by personal interviews. Many studies were not designed primarily to investigate the relationship of nonnutritive sweeteners to bladder cancer. Questions on saccharin were added to these studies as an afterthought. This may have led to some features in study design or data analysis which appear as methodologic flaws.

Using a mail questionnaire survey, Simon et al. (1975) investigated the effects of cyclamate and saccharin in white females with lower urinary tract cancer and in controls with no urinary tract diseases. Sixty-two percent of the cancer cases responded and 60% of the controls, resulting in 135 cases and 390 controls. Each cancer case was matched with a control that had been treated in the same hospital. The controls were also matched with the cases on year of birth within 4 years, urban or rural domicile, and hospital discharge within 2 years of the diagnoses of the bladder cancer. The risk ratio for cyclamate use was 1.2 for both coffee and tea drinkers which did not differ significantly from 1. For saccharin the risk ratio was 1.0.

Morgan and Jain (1974) conducted a similar mail questionnaire survey comparing artificial sweetener consumption in bladder cancer cases with that in two matched noncancer control groups composed of males with benign prostatic hypertrophy and females with stress incontinence. Morgan and Jain provided neither the dates of the study nor the source of the cases and controls. The response rates were 69% for cases and 57% for controls. Seventy-four female and 158 male cases were matched with the same number of controls of the same sex and age. The risk ratio for women was 0.35, which could have been due to chance less than 1 in 100 times, while the risk ratio for men was 1.0, the expected value when the null hypothesis is true. In the other four case-control studies, saccharin consumption was determined directly from interviews rather than mail questionnaires.

Kessler (1976) conducted a matched case-control study of bladder cancer and artificial sweetener use. All subjects were residents of Baltimore who had been discharged from local hospitals from 1972 through

1975. The controls were matched to the cases by sex, race, age, marital status, and hospital. There were 157 male pairs and 52 female pairs, but the rates of participation in the study were not given. There were no statistically significant differences for either sex (or both sexes combined) in the proportion of nonnutritive sweetener users, in mean intake of nonnutritive sweeteners per day, or in the number of mean years that nonnutritive sweeteners were used. Furthermore, there were no statistically significant differences in the use of diet beverages, although the proportion of females who used diet colas, tablets, and powders was greater in the controls than in the cancer patients.

Recently Kessler and Clark (1978) expanded Kessler's 1976 study. Of the 1,300 bladder cancer cases that had been identified, 509 (39%) had died before they could be interviewed, 115 (9%) refused to participate in the study, and 157 (12%) were unprocessed for various reasons. There were a total of 1,038 study subjects, 365 male pairs and 154 female pairs. The results of the study showed the use of all nonnutritive sweeteners to be as follows: for males the matched odds ratio was 0.97, for females it was 1.00, and for both sexes the ratio was 0.98. The risk ratios for saccharin were 1.13 and 0.82 for males and females, respectively, neither of which is statistically significant. These data are consistent with no risk of excess bladder cancer attributable to saccharin. When estimating risk, the investigators omitted the use of nonnutritive sweeteners during the year prior to the diagnosis of cancer. Adjusting for possible confounding by smoking, occupation, age, race, sex, history of diabetes, marital status, education, weight, dieting, and memory, the risk remains unchanged. Although the invesigators stated that the cases and controls were matched for marital status, they did not

explain the differences in that variable that were reported in their study. For both saccharin and cyclamates the controls reported greater mean years of use than did the cases of both sexes. The one statistically significant finding was that male nonsmokers had an adjusted risk ratio of 2.61. A single result this large is expected because of sampling variation in a study with a large number of comparisons; one out of 20 comparisons is expected to be significant by chance alone.

From 1969 to 1974 Wynder and Goldsmith (1977) studied 574 male and 158 female bladder cancer patients and the same number of controls that had been matched for sex, race, hospital, and age at diagnosis. Although subjects had been selected from 17 hospitals in six American cities, 46% had been patients at Memorial Hospital in New York City. Ninety-six percent of the cases and controls agreed to participate in the study. Controls had no previous or present tobacco-related disease, e.g., heart and lung diseases. Questions concerning artificial sweeteners were asked only during the 1973-1974 portion of the study. This produced a limited case group of 132 males and 31 females and a control group of 124 males and 29 females. No statistically significant differences in artificial sweetener use were found.

Howe et al. (1977) compared the use of artificial sweeteners among 480 male pairs and 152 female pairs that were matched for age (within 5 years) and residential neighborhood. The patients with bladder cancer had been diagnosed between April 1974 and June 1976. They were identified through three Canadian provincial cancer registries and through information received from pathologists and urologists. Of 821 eligible cases, 632 (77%) participated in the study. Eighty percent of the controls responded

in British Columbia, 96% in Nova Scotia, and 100% in Newfoundland (Miller and Howe, 1977). In females, there was no increased risk of bladder cancer associated with the use of artificial sweeteners (matched risk ratio 0.6), while males using sweeteners had a bladder cancer risk that was greater than that in controls who did not use sweeteners (matched risk ratio 1.6). The finding for females was not statistically significant, but that for males was highly significant ($p < .01$). These significant results were observed only for the use of tablets or drops of sugar substitutes, but not for diet drinks or saccharin-containing foods. When controlling for the known or suspected confounding variables--education, high risk occupations, history of bladder or kidney infections, smoking combined with consumption of instant coffee, and use of a private water supply--the risk ratio remained stable. This suggests that the risks were not due to confounding by these variables. The authors examined three levels of use of tablets per year: never, < 2,500, and ⩾ 2,500. The The resulting risk ratio showed an increasing gradient of 1.0 to 1.5 to 2.1. The duration of use showed a risk gradient of 1.0 to 1.4 to 2.0 for never, < 3 years, and ⩾ 3 years. Howe and his colleagues reported an unmatched risk ratio of 5.3 for those who used tablets for more than 3 years and for those who used more than 2,500 tablets per year, compared to nonusers. Using the method of Cole and MacMahon (1971), they estimated the bladder cancer incidence in Canadians attributed to the use of all artificial sweeteners to be 7% of all bladder cancer found in males. At current exposure levels this is comparable to an estimate of 3,000 bladder cancer cases in males each year in the United States.

Case-Control Studies: Spontaneous Abortion

Kline et al. (1978) tested whether the use of saccharin as a tabletop sweetener during pregnancy was associated with spontaneous abortions. They studied women who had been admitted for a spontaneous abortion at three New York City hospitals between 1974 and 1976. Controls were mothers who had delivered after 28 weeks of gestation and had been patients at the public prenatal clinics of the same hospitals. They were matched by age (within 2 years) at the most recent menstrual period. Ninety-seven percent of the cases and 94% of the controls participated in the study. Five hundred seventy-four cases and 320 controls were interviewed; 29 cases and 12 controls were excluded because they reported a history of diabetes, their history of diabetes was unknown, or there was no information on body weight. Both cases and controls reported about 6% use of sugar substitutes during pregnancy. The data were adjusted for age, previous pregnancies ending in spontaneous abortions, smoking, and body weight. However, no statistically significant results were obtained. There were several deficiencies in this study. For example, there was no adjustment for social status, as measured by income, which was higher among cases. Furthermore, the questionnaire neglected to ask about several other parameters: the use of other artificially sweetened foods (e.g., soft drinks), the respondent's saccharin consumption before pregnancy, the saccharin consumption habits of the fathers, and any occupational exposure of the mothers.

Evaluation of Epidemiologic Studies

The relationship between saccharin and disease risks has been examined mostly through case-control studies of bladder cancer (Howe et al., 1977; Kessler, 1976; Kessler and Clark, 1978; Morgan and Jain, 1974; Simon et al.,

1975; Wynder and Goldsmith, 1977). The exception is the above-mentioned study of spontaneous abortion (Kline et al., 1978). In all of these studies, the saccharin exposure information has been obtained by questionnaires with known shortcomings such as biased responses due to differential recall and interviewer bias in the assessment of exposure.

Assuming that saccharin is a carcinogen of low potency in humans and that it produces a risk as low as that suggested by Howe et al. (1977), the numbers of bladder cancer cases studied have been too small (Kessler, 1976; Simon et al., 1975; Wynder and Goldsmith, 1977) to demonstrate a statistically significant difference. Furthermore, the cases were often matched with controls but matching was ignored in the analysis (Kessler, 1976; Simon et al., 1975; Wynder and Goldsmith, 1977). This may result in an underestimate of the actual risk.

Since the respondents' medical status could be easily distinguished (or was known by the questioner), the possibility of interviewer bias exists in all retrospective questionnaire studies without an independent assessment of exposure. For example, the interviewer may have tried to "coax the desired response" from the cases with more enthusiasm than he or she portrayed to the controls. This criticism can be made of any study that is built on personal interviews and has been mentioned by the FDA/NCI Interagency Saccharin Working Group (USDHEW, 1977) in a critical review of Kessler's study (Kessler, 1976; Kessler and Clark, 1978).

There is the possibility of selection bias in the use of volunteer controls whose exposure characteristics may differ radically from those of nonparticipants (Howe et al., 1977; USDHEW, 1977). Similar criticisms can be made when hospitalized or private patients from specialty practices are used as controls (Kline et al., 1978; Morgan and Jain, 1974). Both

social and health characteristics of these individuals may differ dramatically from those of the cases. For example, hospital controls in case-control studies of saccharin may not be appropriate because a high proportion of patients are being treated for diseases that are related to obesity; hence, their saccharin intake may not be representative of the general community (Kessler, 1976; Kessler and Clark, 1978). Mail questionnaires may lead to biased selection not only because the most advanced cases may die before they can respond, but also because mail surveys generally have poor response rates (Morgan and Jain, 1974; Simon et al., 1975). The deaths of advanced cases can also hamper a study that is conducted by personal interviews (Kessler, 1976; Kessler and Clark, 1978). Case selection may also be biased in a variety of ways, e.g., by giving preference to the most easily treated or surviving patients (USDHEW, 1977; Kessler, 1976; Kessler and Clark, 1978; Wynder and Goldsmith, 1977). These selection factors will introduce bias in an estimate of risks if saccharin is associated with earlier mortality due to greater malignancy of the tumors.

The possibility of recall bias exists among cases and controls in every study that is based on questionnaires (Howe et al., 1977; USDHEW, 1977; Kessler, 1976; Kessler and Clark, 1978; Kline et al., 1978; Morgan and Jain, 1974; Simon et al., 1975; Wynder and Goldsmith, 1977). Subjects may search for a cause to explain their disease thereby recalling their saccharin use in greater detail, whereas controls may overlook some saccharin consumption when responding to the interviewers' questions.

Adjustments may not have been made for some confounding variables such as smoking, occupation, coffee consumption, medical history, social status, and type of water supply (Cole, 1975). This oversight could lead

to a spurious estimate of risk (USDHEW, 1977). Although Howe et al. did adjust for these variables, they were severely criticized for using a dichotomous assessment (e.g., dividing each category of confounding factors into two simply defined groups) rather than interval or continuous measurements (e.g., finer measurements of cigarette use and coffee consumption [Anonymous, 1977]). Miller (one of Howe's coauthors) responded to this criticism by expanding the consideration of variables to place of residence (by province), instant-coffee consumption, and cigarette smoking. These additional factors did not alter the risk substantially (Miller and Howe, 1977). A brief presentation of adjustment procedures makes analysis of possible confounding factors difficult, as in the study by Howe et al. (1977). To study spontaneous abortion it seems important to obtain information about consumption of all foods containing saccharin (especially soft drinks) by females before pregnancy and by the fathers (Kline et al., 1978).

Synergy should be addressed (Hicks and Chowaniec, 1977; USDHEW, 1977) when considering multiple exposures among saccharin users. Such exposures are likely to include cigarette smoking, coffee drinking, and a history of hazardous occupational exposure.

Latent times for malignancy are commonly measured in decades, and periods of 30 to 40 years may be required for the total effect of any carcinogen to become apparent in humans. A common problem of all the studies on humans to date is that the major increase in use of saccharin may be too recent for its carcinogenic effects, if present, to be manifest.

Epidemiologic Studies in Progress

Citing several weaknesses in study design (as noted above), the FDA/NCI Interagency Saccharin Working Group has recently initiated a large case-

control study to determine the risk of bladder cancer resulting from the use of saccharin (USDHEW, 1977). Investigators will be informed of newly diagnosed bladder cancer cases from nine centers of the Surveillance, Epidemiology, and End Results (SEER) network. This is a system of tumor registration of the Biometry Branch of the National Cancer Institute, which encompasses the states of Connecticut, Iowa, New Mexico, and Utah, and the cities of Detroit, San Francisco-Oakland, New Orleans, Seattle, and Atlanta. For this study, incidence data will be obtained also from the tumor registry of New Jersey. There will be approximately 4,200 cases and 8,400 controls in the study. The large number of subjects will make it possible for even small risk differences to be statistically significant. Predictions indicate that 60% of the cases will be older than 65 years, 75% will be male, and most participants will be white.

The controls will be selected from a random sample of the population. They will be stratified so that they have the sex, race (white and non-white), and age composition of the general population in each study location. Controls older than 65 years will be randomly selected from the records of the Health Care Financing Administration. Controls younger than 65 will be selected by random-digit-dialing.

Cases and controls will be asked to respond to a questionnaire that will be administered in their homes by trained interviewers. The question will cover the following subjects because of suspected relations with bladder cancer.

- Lifetime residential history
- History of drinking water used (public, well, and bottled)
- Lifetime occupational history

- History of tobacco use (especially cigarettes)
- Types and amounts of fluid consumption 12 months ago to avoid the measurement of any change since diagnosis
- History of nonnutritive sweetener use
- Medical history (such as diabetes or bladder disease)
- History of hair dye use
- Other demographic information

If resources permit, the nonrespondent cases and controls will be compared to those who enrolled in the study.

The study will employ regression analysis to assess the risk from many variables simultaneously (Miettinen, 1975). This will permit the estimation of relative risk by the calculation of risk ratio (or odds ratio) while controlling for the effect of confounding variables. The method allows one to evaluate different levels of risk, thus making it possible to indicate whether artificial sweeteners interact with certain other factors (Hicks and Chowaniec, 1977). Finally, the percent of bladder cancer mortality attributed to saccharin (known variously as the "etiologic fraction" or "population attributable risk percent") can be estimated (Cole and MacMahon, 1971).

Potential Sources of Data

Although prospective studies are very costly (in money and time) in comparison with retrospective case-control studies, the availability of prospective data sources might be a way to assess dose-response relationships and to adjust for confounding factors. To avoid biased recall, which can occur in retrospective studies, the nonnutritive sweetener exposures should be assessed in nondiseased individuals. To do this, an epidemiologist might undertake a prospective study in which a sample of

healthy users and nonusers of saccharin are followed for a sufficiently long period to observe tumor incidence. After a certain time, a measure of the relative risk among saccharin users could be obtained by comparing the rate of bladder cancer (or perhaps some other disease) among the users with that of the nonusers. There are several possible options:

Diet Studies. Disease risk (thought to be bladder cancer) can be evaluated in individuals whose diets were thoroughly measured. Some possible sources are:

- the combination of several heart disease studies in which dietary data are or were being collected. Examples are the Framingham, Mass. (Dawber et al., 1951), Tecumseh, Mich. (Francis and Epstein, 1965), Evans County, Ga. (Hames, 1971), Multiple Risk Factor Intervention Trial (MRFIT Group, 1977), Lipids Research Clinics (University of North Carolina, 1974), and Hypertension Detection and Follow-up Project (Borhani et al., 1976; Castle et al., 1977). The problems are a lack of consistent protocol for measuring diet, insufficient sample sizes to obtain enough cancer cases among saccharin users, and, in the last three studies, an insufficient period of determination for many cancer cases to be detected.
- a subpopulation of known nondiabetic users of artificial sweeteners, such as members of a self-help diet group. The risk of disease in this group could be compared to the population as a whole if adjustments are made for the sequelae of obesity. The morbidity and mortality profiles of cardiovascular diseases in the obese are similar to those in diabetics. Hence,

using this group to examine the association between saccharin and cancers may have the same disadvantages as those encountered in studies with diabetics.

- a national survey of food and nutrition from which responses about nonnutritive sweetener use were obtained. There are two extant studies for which a follow-up might provide a reliable risk estimate: a 1965 U.S. Department of Agriculture (USDA) survey of foods with 14,000 respondents (with approximately 400 saccharin users) (USDA, 1972), and a 1971-1974 study of food and nutrition with 20,000 respondents by the National Center for Health Statistics (NCHS) which obtained the frequency of saccharin use and smoking data (with approximately 2,600 users) (USDHEW, 1978a). There was also a survey with 27,000 respondents which was conducted in Canada (Canadian National Health and Welfare Ministry, 1976), but officials do not feel that the data on the use of nonnutritive sweeteners are valid.

From these data the relative risk can be obtained by comparing all users with a sample of nonusers to develop a profile of causes of death. Calories can be correlated to determine if there is a relationship between nonnutritive-sweetener use and the amount of caloric intake.

The greatest difficulty in a prospective study is obtaining a large enough sample of saccharin users. Working from Schlesselman's estimates of sample sizes, a prospective study would require 139,946[1] artificial sweetener users (or person-years of use) and the same number of nonusers to show a relative risk of two (Schlesselman, 1974). If the relative risk were four, the required number of users would have to be 17,804[1] with an

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[1] This assumes an $\alpha = 0.05$ (1-sided) and $\beta = 0.3$ and a probability of bladder cancer mortality of one in 10,000 for those aged 35 years and over.

equal number of nonusers. Unless the subjects were already enrolled in a survey and their vital status could be determined, such a study might be too costly and too time-consuming to estimate efficiently the bladder cancer risk for saccharin users. A further concern is that a sufficiently long time interval (commonly referred to as "latent period") from exposure to disease onset may not have passed. The efficiency of the study can be enhanced by matching for confounding variables (Schlesselman, 1974). This would reduce the number of study subjects somewhat, but the cost of individually matching saccharin users with nonusers on the known confounding variables is likely to be prohibitive. Group matching may be a viable alternative.

Occupational studies. Occupational studies on workers who are involved in the production or handling of saccharin offer the prospect of studying humans with the greatest potential exposure. Before the introduction of improvements in industrial hygiene, exposures were likely to be heaviest in areas where saccharin is dried and processed. Systemic exposure could have occurred through the dermal, gastrointestinal, or pulmonary routes.

Occupational studies can address many confounding factors such as age, sex, social class, and previous medical disability (Goldsmith, 1975; McMichael, 1976). However, they may be unable to separate the interactive effects of other chemical exposures, cigarette smoking, and previous non-occupational exposures. The central question is whether exposure data are available or whether surrogate instruments for estimating exposure could be developed (Gamble and Spirtas, 1976). There is one study of chemical company employees who have been involved in the manufacture of saccharin for many years, but results are not yet available. Unlike the

automated production process in another company, which employs only 13 workers, there were 330 workers employed over a period of 70 years until saccharin production stopped in 1972. These workers might show an elevated standardized mortality ratio when compared with the U.S. male bladder cancer rates (McMichael, 1976).

An occupational study could be approached either retrospectively or prospectively. If a retrospective case-control study design were used, a sample size of 188 bladder cancer cases and an equal number of controls would be required to show that work in the saccharin production area resulted in a statistically significant odds ratio (i.e., risk ratio) of two (Schlesselman, 1974). If the odds ratio estimate were four, only 45 cases and 45 controls would be required, assuming $\alpha = 0.05$, $\beta = 0.10$, and a general exposure to saccharin in the plant that is equal to 30% (Schlesselman, 1974). Only Kessler and Clark (1978) and Howe et al. (1977) studied enough cases to show a risk ratio of two with the same assumptions.

Most suggestions for prospective studies appear promising, but are unlikely to provide any useful epideniologic data because fruitful studies require long observations which would preclude production of useful data within the near future. A retrospective study of occupational cancer(s) among saccharin production workers may be feasible in terms of cost and time and may provide additional data on other disease outcomes, if the number of subjects is adequate to attain appropriate sensitivity.

Male/Female Risk Differences

The present studies on saccharin carcinogenesis in humans (Howe et al., 1977; Kessler and Clark, 1978; Morgan and Jain, 1974) and in animals (DHEW, 1973a,b; Canadian National Health and Welfare Ministry, 1977b; Tisdel et al., 1974) suggest an elevated bladder cancer risk for

males and a decreased risk for females. This anomaly exists in spite of the repeated observations that females consume more saccharin-sweetened beverages than do males. Clearly, this raises another issue. For example, is the modifying effect of sex due to the hormonal difference between sexes or some other distinguishing characteristic, including different exposures? Appropriately designed, prospective studies of humans may assist in identifying the metabolic, hormonal, or other characteristics that cause the difference in risk between the sexes.

SUMMARY

The committee reviewed the epidemiologic studies of the relationship between saccharin and bladder cancer and between saccharin and spontaneous abortion (Table 3-11). With one exception, findings indicated the absence of a health hazard for either sex. However, there were many deficiencies in the methods of the studies that showed no association. Two studies by Howe et al. (1977) and Kessler and Clark (1978) are of sufficient sensitivity to measure a relationship. The study by Howe et al. (1977) showed a statistically significant increase in risk (risk ratio of 1.6) for bladder cancer in males and no significant effect in females. The findings of this study were analyzed to determine if any confounding factors had been overlooked, but none were found. Howe et al. also reported an increasing risk of bladder cancer with increasing amounts of saccharin used, duration of use, or both. In contrast, the study by Kessler and Clark (1978) showed a 1.1 relative risk factor for males, not considered statistically significant, and no association for females.

The committee suggests two alternative data sources that could be

TABLE 3-11

Summary of the Epidemiologic Studies of Saccharin and Bladder Cancer

Reference	Source of Data on Saccharin Exposure	Comparend	Type and Years of Study	Measure of Effect	95% Confidence Intervals or Probability Value
Armstrong and Doll, 1974	Annual U.K. bladder cancer rates	Saccharin consumption patterns	Time-trend 1911-1970	Expected association not found with high consumption during World War II	
Burbank and Fraumeni, 1970	Annual U. S. bladder cancer rates	Cyclamate-saccharin consumption patterns	Time-trend 1950-1967	No clear association with rise in consumption during 1960's	
Armstrong and Doll, 1975	Bladder cancer death certificates mentioning diabetes:	Other cancers (excluding lung and pancreas) mentioning diabetes:	Case-control 1966-1972	Relative frequency of diabetes:	
	138 males 81 females	138.0 males 81.6 females		1.00 males 0.97 females	0.62-1.60 0.59-1.58
Armstrong et al., 1976	Of 5,971 members of the British Diabetic Association, the number dying of bladder cancer was:	Expected bladder cancer mortality for England and Wales, 1972:	Prospective 1965-1973	Standardized mortality ratio:	
	4	5.8		70	0.19-1.79
Kessler, 1970	Bladder cancer deaths among whites for whom diabetes had been diagnosed at the Joslin Clinic from 1930-1956:	Massachusetts, age- and sex-specific death rates, 1931-1959. Expected bladder cancer deaths:	Retrospective case-control 1930-1960	Standardized mortality ratio:	
	14 males 7 females	18.1 males 11.5 females		77 males 61 females	p >.3 p >.1
Simon et al., 1975	White female bladder cancer patients from collaborating hospitals, Boston:	White female patients with non-urinary tract diseases:	Matched case-control 1965-1971	Risk Ratio: [a]	
	135	390		1.0	p >.1

Morgan and Jain, 1974	Hospitalized bladder cancer patients:	Benign prostatic hypertrophy:	Matched case-control Dates not given	Risk ratio:	
	158 males	158 males		1.0	p >.1
		Problems of stress incontinence:			
	74 females	74 females		0.35	p <.01
Kessler, 1976	Bladder cancer patients from 19 cooperating Baltimore hospitals:	Noncancer patients:	Matched case-control Dates not given	Rate ratio:[a]	Not given
	157 males	157 males		0.74	
	52 females	52 females		1.65	
Kessler and Clark, 1978	Bladder cancer patients from 19 cooperating Baltimore hospitals:	Noncancer patients:	Matched case-control 1972-1975	Rate ratio:	
	365 males	365 males		1.11[b]	0.75-1.58
	154 females	154 females		0.80[b]	0.47-1.39
Wynder and Goldsmith, 1977	Patients with bladder cancer in 17 U.S. hospitals (46% from Memorial Hospital in New York):	Patients with no previous or present history of tobacco-related disease	Matched case-control 1973-1974	Rate ratio:	
	132 males	124 males		0.74	0.2- 2.2[c]
	31 females	29 females		0.71	0.1-10.0[c]
Howe et al., 1977	Patients in three Canadian provincial tumor registries:	Matched neighbor control:	Matched case-control study April 1974-June 1976	Matched risk ratio:	
	480 males	480 males		1.6	1.1-2.3
	152 females	152 females		0.6	Not given

[a] Matching ignored.
[b] Adjusted for smoking, occupation, age, race, sex, diabetes, marital status, education, overweight, dieting and memory using multiple loxistic method.
[c] Approximately.

used to assess the risk of saccharin: data from prospective studies in which accurate dietary information was collected and surveys to assess the risk of bladder cancer in workers who are involved in the production and handling of saccharin. These workers might be compared with those employed in other areas of the same plant.

CONCLUSIONS

(1) Time-trend studies provide no evidence that saccharin use is necessarily associated with cancer (Armstrong and Doll, 1974; Burbank and Fraumeni, 1970). This method may be too insensitive to separate the effects of saccharin from known bladder cancer risk factors, such as cigarette smoking, that have also been changing over time.

(2) Studies on diabetics (Armstrong et al., 1976; Armstrong and Doll, 1975; Kessler, 1970) do not show a positive association between saccharin use and bladder cancer but these studies suffer from a number of limitations which hinder assessment of the risk of saccharin: (a) findings in diabetics may not be applicable to the nondiabetic population; (b) individual saccharin consumption was not measured; and (c) there were no data on differences between diabetics and the general population with respect to smoking habits and certain occupations that are known to be associated with bladder cancer.

(3) The case-control studies do not provide clear evidence to support or refute an association between saccharin use and bladder cancer. Two studies of sufficient size for reliable

measurement of low level effects of saccharin use are those by Howe et al. (1977) and Kessler and Clark (1978). The study by Howe et al. used a complex method to estimate the relative risk of bladder cancer in nonnutritive sweetener users and nonusers. This study reported that the proportion of male bladder cancer patients who used nonnutritive sweeteners is significantly higher (risk ratio of 1.6) than the proportion of male controls who used nonnutritive sweeteners. The study by Kessler and Clark (1978) reported no statistically significant excess risk for either sex, and is thus consistent with no excess cases of bladder cancer attributed to the use of saccharin. The committee believes that the methodologic difficulties of each study do not allow one to judge the seemingly contradictory results. Four other studies have failed to demonstrate a statistically significant risk (Kessler, 1976; Morgan and Jain, 1974; Wynder and Goldsmith, 1977; Simon et al., 1975), but these have major deficiencies which severely limit confidence in their findings.

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CHAPTER 4

BENEFITS OF SACCHARIN

The committee wishes to draw attention to the difficulty in assessing the variety of benefits ascribed to saccharin. Some individuals have suggested that saccharin is beneficial to health because it may aid in the maintenance of desirable body weight or in the prevention of dental caries (Stunkard, 1977; Nizel, 1977). Other groups consider saccharin to be important in facilitating weight reduction (Lee, 1978), control of diabetes (American Diabetes Association, 1978), or promotion of the proper use of prescribed drugs (Feldman, 1977). Numerous psychological benefits have also been attributed to the use of saccharin (U.S. Congress, 1977a), all related to the desire for sweets. These range from conformity to cultural patterns to, simply, aesthetic pleasure. The committee's efforts to examine these issues have been severely hampered by the lack of scientific evidence pertaining to health benefits, the difficulty in measuring perceived benefits, and the prevalence of the conflicting but strongly held views among professionals and the general public.

Discussions concerning the benefits of saccharin have gathered considerable momentum since the Food and Drug Administration's (FDA) proposed ban in March 1977. The committee's decision to evaluate the benefits is largely the outcome of public and congressional concern that the beneficial effects of saccharin have been ignored in the proposed ban. This is evident from the Saccharin Study and Labeling Act (U.S. Congress, 1977b), which specifically mandates a study of "the health benefits, if any, to humans resulting from the use of nonnutritive sweeteners in general and saccharin in particular." This is especially relevant since saccharin is the only nonnutritive sweetener (NNS) currently permitted in the American food supply.

For the past 50 years, the use of saccharin has increased in the United States, and the consumption of saccharin per capita has nearly doubled in the last 7 years. Today, it is commonly used in diet drinks and desserts, canned fruits, candy, gum, drugs, cosmetics, toothpaste, and as a tabletop substitute for sugar. Its daily use by several generations of Americans (in 1968 users of NNS's were estimated to be approximately 20 million [Crampton, 1975]) has made saccharin an integral part of the American lifestyle.

The proposal to ban saccharin has been subjected to sharp criticism from several quarters. Two nationwide public opinion polls, which surveyed approximately 1,500 adults in both April and June 1977 (Harris, 1977a,b), reported opposition to the ban by a margin of approximately 5 to 1. Similar findings were obtained from a questionnaire given to 389 individuals in January 1978 (Parham, 1978). In Canada, where saccharin has been banned as a food additive since 1977, leading medical associations have made a concerted effort to examine the pros and cons of the restriction (Canadian Diabetic Association, 1977; Canadian Medical Association, 1977; Roydhouse, 1977), have formed a committee to contend with the issue (Canadian Ministry of Health and Welfare, 1977), have suggested alternatives, or have provided guidelines for the use of saccharin (Hollands and Goeller, 1977). In the United States, a similar response has been made by some institutions (American Dietetic Association, 1977), but a number of professional and consumer-oriented organizations are skeptical about the ban. For example, the American Diabetes Association (1978) and the American Dental Association (1978) have questioned the advisability of the ban, and the Calorie Control Council, a representative of the industrial users of saccharin, has lodged protests against the FDA's proposal (Gelardi,

1977). Numerous objections have been based on the assumption that the risk to human beings of cancer from saccharin has not been established, that the scientific data collected so far are inconclusive, and that the benefits of saccharin far outweigh its supposed risk.

Despite such assertions, it has not yet been established whether saccharin leads to measurable health benefits. Furthermore, a recent report on saccharin by the Office of Technology Assessment (U.S. Congress, 1977a) indicates that the potential benefits of saccharin have not been subjected to the same kind of scrutiny that has been given to its risks. This may be explained partly by a historical perspective. In permitting the use of food additives, the FDA has emphasized the establishment of a safety record (i.e., the absence of ill effects) by toxicity testing rather than by demonstrating a direct benefit. According to the Food Additives Amendment, direct food additives must satisfy two essential criteria. First, there must be proof that the additive is safe under conditions of intended use and that it will not cause adverse effects on the health of consumers. Second, the substance must be functional or capable of accomplishing its intended technical effect. A determination of the value of the effect and, thus, a proof of its direct or indirect health benefits are not required and, in previous legislation, has been explicitly excluded. Consequently, a methodology for assessing benefits has not been developed.

There is a noticeable paucity of relevant literature on benefits. Moreover, there is no clear definition of what would constitute a benefit or how to measure it. Particularly evident is the lack of a rational yardstick for comparing inherently different dimensions, e.g., the number of lives saved versus dollars expended or perception of immediate pleasure

and improved quality of life versus future risk of disease. Similarly, there is no system for obtaining an overall estimate of benefit. This is pertinent because many of the benefits attributed to saccharin are subjective, e.g., improvement in taste or psychological well-being. As such, benefits are evaluated in different terms than are risks, and they are generally harder to quantify. However, there is a parallel. While risk to animal species may be demonstrable quantitatively through experimentation, extrapolation of the potential risk to humans requires judgment in the absence of conclusive epidemiologic data. Similarly, potential benefits may be implied subjectively or assessed objectively through clinical trials. The latter involves a different extrapolation, usually from an inadequate data base alone or combined with the experience and observation of the investigators. Therefore, while objective assessment of risk and the computation of benefit are both necessary, both involve some subjective steps in the extrapolation process, to different degrees.

The benefits of saccharin cannot be assessed in isolation. They must be regarded in view of the incremental risk posed by the consumption of saccharin (see Chapter 3), the consequences of its removal from the market, and whether alternative sweeteners exist. At the outset, it would be important to consider the potential benefits of saccharin to health, in terms of both maintenance of health and the prevention and treatment of specific disorders. Subsequently, it would be necessary to examine the origin of the desire to use saccharin. Perhaps this desire could be expressed in no more complex a concept than the human preference for sweet substances.

The potential benefits of saccharin to health are discussed below, followed by a summary of related economic considerations.

POTENTIAL BENEFITS OF SACCHARIN

Health Maintenance

Weight Control. Although the importance of preventing weight gain in individuals of normal weight is less obvious than the need for intervention to produce weight loss, the prevention of weight gain may be quantitatively more significant in the long run. A large number of saccharin users have indicated in a recent poll that saccharin aids them in maintaining their normal body weight and physical appearance (Market Facts, Inc. [MFI], 1978a). However, clinical trials to test this perception or to study the value of nonnutritive sweeteners in weight maintenance have not been conducted. The few investigations of the impact of NNS's on the energy balance have focused on weight reduction in overweight subjects. Nonnutritive sweeteners provide a means of satisfying the desire for sweetness without an increase in the consumption of energy (calories) that accompanies the ingestion of sucrose or other sugars. Thus, despite the lack of scientific data that are needed to demonstrate either the extent or the value of NNS's in weight maintenance, the availability of saccharin may theoretically provide the informed consumer with an option: that of ingesting larger quantities of highly desired foods or of reducing sugar intake without foregoing the desire for sweetness.

Prevention of Dental Caries. Saccharin is thought to assist indirectly in preventive dental care. This assumption stems from the concern that the substitution of sucrose in dentifrices and soft drinks may exacerbate the incidence of dental caries--a public health problem of major proportion in the United States. In addition, saccharin is used commonly as a sweetening agent--an additive considered to be necessary

in promoting the use of dentifrices. Not only is dental caries the leading chronic disease in children, it affects over 98% of the population of all ages (Keene et al., 1971). Even at its present level of incidence, it poses a significant economic burden. For example, an estimated $10.04 billion was spent by the public in 1977 for dental care. Much of this was required to repair the damage of caries. Even so, less than half the population obtains any dental treatment (USDHEW, 1972).

A brief review of the etiology of dental caries will assist in the evaluation of the potential benefits of saccharin and other NNS's to dental health.

Dental caries results from the interaction among certain oral bacteria, a tooth whose susceptibility is believed to be due largely to a lack of fluoride in the tooth enamel, and the presence in the mouth of highly fermentable carbohydrates, which the bacteria metabolize to organic acids. There is convincing evidence that sugar, especially sucrose, is the major dietary contributor to the incidence of caries (Newbrun, 1967). Oral bacteria, especially Streptococcus mutans (a prime microbial agent in the pathogenesis of caries), convert sucrose to acid and to complex polyglucans, which are sticky and insoluble and facilitate adhesion of bacterial plaque to tooth surfaces. Studies on animals show that less frequently consumed saccharides, including glucose and fructose, are also highly cariogenic (Green and Hartles, 1969).

It is now widely accepted that the frequency of sugar consumption (thus, the frequency of acid attack upon tooth enamel) and the form in which sugar is consumed are more important in the causation of caries than the actual amount of sugar consumed. Therefore, efforts to prevent caries by altering the dietary factor in caries etiology focus upon reducing the

frequency of sugar consumption, especially in between-meal snacks and beverages.

Studies on animals have demonstrated that a reduction in the frequency and amount of sucrose that is ingested results in decreased incidence of caries. This has been confirmed in epidemiological surveys (Takeuchi, 1960; Toverud, 1950) as well as in controlled trials with humans (Gustafsson et al., 1954; Harris, 1963). In a recent, well-controlled study in Finland, volunteers consumed a diet in which practically all sucrose was replaced by the polyol, xylitol. When compared to controls who consumed a normal, sucrose-containing diet (Scheinin et al., 1975), the volunteers showed an approximately 90% reduction in the incidence of caries after 2 years. However, a recent preliminary report from England linking xylitol with bladder cancer in animals has raised questions about the utility of xylitol as a sweetener in foods (J. Carlos, Huntington Laboratories, personal communication, 1978).

Because saccharin is nonfermentable and does not support bacterial growth, one may assume that it is noncariogenic. Therefore, it may have potential benefits as a sugar substitute in snack foods or sweet beverages that frequently contact the surface of teeth. Saccharin is widely used as a sweetener in dentifrices, usually at a level of approximately 0.2%. Nizel (1977) estimated that the amount of saccharin ingested from dentifrices is from 100 to 1,600 times less than that consumed from a single soft drink. This would imply a negligible risk factor compared to the potential increase in the incidence of caries should cariogenic sugars (such as sucrose) be substituted in snack foods. Dentifrices containing fluoride reduce the incidence of caries by 15% to 25% (Horowitz and

Heifetz, 1975). To the extent that saccharin improves the taste, thereby promoting the use of such dentifrices, additional health benefits may be inferred.

Specific efforts to study the efficacy of saccharin in the prevention of dental caries have been limited. Linke and Chang (1976) studied the influence of four nutritive sweeteners and five artificial sweeteners on the growth pattern of Streptococcus mutans in vitro in a glucose medium. Sodium saccharin in concentrations of 0.02 to 20 mg/ml had a definite growth-inhibiting effect, the magnitude of which was proportional to the concentration of saccharin. The authors implied that saccharin may have a potential use in the prevention of caries.

Grenby (1975) studied 24 student volunteers receiving a diet that was sweetened with a mixture of saccharin and up to 98% glucose for 3 days. An average of 42 g of sweetener per person per day was consumed. He noted that the amount of dental plaque that formed was significantly less than that in the control subjects using sucrose. It is not clear whether the reduction in plaque was due to the substitution of glucose (considered to be slightly less cariogenic than sucrose [Green and Hartles, 1969]) for sucrose or whether it was due to saccharin, because the effects were not measured separately and the amount of saccharin in the sweetener was not stated.

One can assume that saccharin is noncariogenic, although there is no direct clinical data to support this. Nevertheless, convincing data suggest that substantial replacement of dietary sucrose by noncariogenic sweeteners will result in a significant reduction in the incidence of caries.

While a single noncariogenic sweetener would probably not have a profound effect on prevention of dental caries, an array of such sugar substitutes used in a variety of foods could have a major impact on this public health problem. Saccharin has definite potential benefit in this context.

Treatment and/or Control of Health Problems

Obesity. NNS's are frequently used as substitutes for sugar on the assumption that they will replace a portion of dietary calories, thereby producing a negative energy balance and weight loss. An important criterion in evaluating the efficacy of NNS's for the treatment of obesity rests in the question, "Does the use of saccharin promote sustained weight loss in the obese?" Theoretically, saccharin may contribute to weight loss if its consumption reduces total carbohydrate ingestion by reducing refined sugar intake. This must occur without a compensatory increase in calories from other food sources, in a free-living situation and over an extended period. Therefore, the relevant question is not could saccharin produce these results, but does it? If it does not, this may indicate simply that the effects of saccharin, although real, are so infrequent or weak that they are outweighed by the other forces that tend to maintain obesity. Genetics, endocrine changes, and neurological, psychological, and social influences are all thought to contribute to the reduction and maintenance of body weight. Several of these factors probably operate to varying degrees in different obese subjects. Accordingly, many modes of therapy for obesity have been explored, most with limited success. These are summarized below:

- Mechanical/anatomical: jaw-wiring, gastric or jejunal bypass surgery, panniculectomy;

- Hormonal:[1] administration of thyroid hormone, or human chorionic gonadotropin;
- Neurological/psychotropic: administration of amphetamines[1] and related drugs; or fenfluramine hydrochloride (Pondimin®);
- Dietary: nutrition education and diet planning to restrict caloric intake or to limit ingestion to certain types of foods, e.g., high protein diet, grapefruit diet, etc.;
- Dilution of caloric density: administration of nonnutritive dietary preparations, e.g., cellulose, NNS, liquid formulas, etc.;
- Psychiatric: psychotherapy, psychoanalysis;
- Behavioral techniques: aversive conditioning, behavior modification based on operant conditioning.

The foregoing discussion makes it clear that NNS's are one component of a single mode of dietary intervention in the treatment of obesity. Consequently, their efficacy should be evaluated in that context.

A few studies report the use of NNS's, including saccharin, for weight reduction (Table 4-1). In a 6-week study by Breslow (1964), saccharin and cyclamates were substituted for sugar in desserts and beverages in the diets of 25 prisoners and of a corresponding numbers of control subjects. The test subjects lost an average of 1.3 kg (males) and 0.9 kg (females) in 6 weeks ($p = 0.05$) as compared to an insignificant gain by the control group. Breslow concluded that weight loss would occur if the diet contains large quantities of sugar for which NNS's could be substituted and

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[1] No longer approved modes of treatment.

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TABLE 4-1

Selected Clinical Trials Using Saccharin and Other Nonnutritive Sweeteners

Reference NNS used	Method	SUBJECTS Type	Age/Sex	No. (controls)	Duration	Dosage	Major Findings	Comments
Breslow, 1964 Cyclamates:saccharin	Fed as sugar substitute to prisoners	Overweight[a]	Adults F M	25 10 (10) 15 (15)	6 weeks	Not stated	Test males lost 3 lb/10 oz and females 2 lb (P=0.05). Control males gained 9.9 oz per person and females 6.2 oz/person (not significant).	Not clear whether all subjects were over weight. Amounts of NNS not stated. No follow-up data reported.
Glenn, 1964 Cyclamates:saccharin	Voluntary intake by private patients	Overweight[a]	Adults	10 (10)	10 weeks	Not stated	Weight loss equalled 0.67 lb/wk including first week or 0.35 lb/wk excluding it.	No controls used. No statistical data given. No weights stated. No follow-up data.
McCann, 1956 All NNS's including saccharin	Questionnaire	Obese Diabetic	Adults Adults	247 (0) 100 (0)	One interview	Not stated	Of 147 obese subjects followed for 3 years, 65% lost weight, but no significant differences between users and nonusers of NNS's.	No data on remaining 100 obese adults regarding weight loss or on diabetics regarding disease control and NNS's.
Alexander, 1962 All NNS's	Questionnaire	Obese	Adults	82 (0)	Not stated	Not stated	No significant correlation between use of special foods and weight loss.	Amounts of NNS's not quantified.
Porikos et al., 1977 Aspartame only	Caloric reduction by covert substitution in sugar products	Obese inpatients	Adults F M	8 (0) 6 (0) 2 (0)	6 days	Not stated	Initially, spontaneous reduction in caloric intake (23%) in test period.	Short duration. Cannot predict behavior of subjects in normal outpatient environment or over long term.
Farkas et al., 1965 All NNS's - Cyclamates and saccharin	Questionnaire	Diabetic	Adults F M	100 (0) 100 (0)	One interview	Not stated	No significant differences in degree of dietary adherence among users and nonusers of NNS.	Amounts of NNS not quantified. No biochemical measures of diabetic control.
Stern, 1967 Cyclamates Cyclamates:saccharin 10:1	Recorded intake of NNS's	Diabetic	Adults	34 (14)	13 mos.	869 mg/day to 3.2 g/day	No significant changes in battery of laboratory tests. No significant differences in group averages for body weight or blood glucose.	No weight loss in obese diabetics despite large doses and prolonged ingestion of NNS. Caloric intake not measured.
Lenner, 1976 Starch/saccharin mixture in breakfast	Feeding test meal with different sweeteners	Diabetic	Adults F M	9 (3) 7 (3) 2 (0)	One meal	Not stated	Starch/saccharin meal led to increase in blood glucose at 60 min compared to sorbitol and fructose but not sucrose.	Amounts of saccharin not stated. Effects of saccharin cannot be separated from those of starch.

[a] Assumed to be overweight, but not stated by author.

if the total caloric intake was controlled. However, it is not clear whether the subjects had a choice of total food quantity, hence, of caloric intake. Furthermore, the author does not indicate whether all the subjects that were studied were overweight and to what extent they were overweight since other anthropometric measurements, e.g., height, skin folds, were not given.

Glenn (1964) studied 10 hospital employees and 10 private patients. Sucaryl (cyclamate/saccharin) was substituted for some of the sugar in the diet for 10 weeks. The average weight loss was 0.3 kg/wk if the first week was included, or 0.16 kg/wk excluding it. The author noted a gradual waning of the desire to diet and a partial return to the pre-study eating habits. In this study, no controls were used, no statistical data were presented, and no patient characteristics were stated. It is not clear if the subjects were overweight at the start of the study.

Both Breslow's and Glenn's studies were of short duration. No follow-up data have been reported.

McCann et al. (1956) surveyed 247 obese nondiabetic adults and 100 adult diabetics to determine the association between the use of NNS's and weight loss. Of 147 obese adults that were followed for 3 years, 65% lost weight. But there was no significant difference in weight loss between the users and nonusers of NNS's. There was no evident relationship between the length of NNS use and the percentage of those who lost weight nor was there a correlation between the degree of overweight and the use of NNS's or artificially sweetened foods. There were no data on weight control for the remaining 100 obese adults or on the control of diabetes for the diabetics with the use of NNS's.

Alexander (1962) distributed questionnaires to 82 overweight adults in outpatient clinics in the Boston area to evaluate the use of dietary aids such as formula diets and NNS's. Ninety percent of the subjects had resorted at some time to at least one special preparation. In this study, none of the special foods used was correlated with dramatic weight loss; in most cases, there was little or none. The author concluded that "reducing" foods do not reduce and that formula diets have not solved the dieter's dilemma.

Two additional studies that were conducted under closely controlled conditions give an interesting perspective to the problem of weight and NNS's. Using three groups of 10 mice each, Friedhoff et al. (1971) studied the effects of spontaneous solid food intake and weight gain by substituting an artifically sweetened solution (6% sodium cyclamate and 0.6% sodium saccharin) for sugar solution in one group. A second group received a sugar solution, and the third group, water, for a period of 23 days. All animals gained weight during the study; however, there were no significant differences among the groups or between any pairs of groups. In the animals drinking the sucrose solution, there was a spontaneous reduction in solid food ingestion. The authors concluded that mice that were given a normal diet and sucrose solution did not gain weight faster than those eating the same diet plus either a NNS or water. This may not necessarily apply to the consumption of beverages by humans, but it does bring into question the value of simple substitution of no-calorie beverages to control weight.

In a similar clinical trial, Porikos et al. (1977) measured the effect of caloric dilution on spontaneous food intake in eight obese

inpatients. The subjects were unaware that their food intake was being monitored. Caloric dilution was accomplished by replacing the sucrose content with aspartame in an otherwise normal diet. No saccharin was used. The study lasted 15 days with a baseline period of 3 days (period I), two 3-day periods (II and III) when aspartame was substituted, and two 3-day periods (IV and V) when the baseline conditions were restored. Caloric intake decreased by 23% in period II and increased slightly during period III. However, it was significantly lower during periods II and III compared to I, IV, and V. Since the aspartame products were indistinguishable in taste, appearance, and texture and were readily accepted by the subjects, the reduction in caloric intake during the test periods was attributed to aspartame ingestion. The subjects gained weight with the sucrose diet and maintained their weight with aspartame. The authors suggested that some obese subjects will not increase spontaneous energy intake sufficiently in 6 days to overcome covertly imposed caloric reduction of approximately 25%. However, the 6-day tests were too short to examine adaptive responses to caloric depletion. Moreover, this study could not predict the behavior of obese outpatients or subjects living at home where many factors could influence weight control.

Diabetes. Saccharin has a potential benefit for diabetics by restricting calories for overweight patients while satisfying a craving for sweets without influencing blood glucose concentrations. Theoretically, saccharin could improve dietary compliance as well. In addition, it would be important to assess whether the consumption of saccharin improves metabolic control in diabetics.

The therapy of diabetes combines dietary and pharmacologic elements. Most adult-onset diabetics are obese. Since obesity exacerbates the metabolic abnormalities of diabetes, dietary therapy in this group is directed primarily toward the normalization of body weight. By contrast, most juvenile-onset diabetics are not overweight. Indeed, many have difficulty maintaining normal weight. Dietary therapy in this group is designed to match food availability to insulin action, prevent hypoglycemic (insulin) reactions, and minimize blood sugar peaks.

Saccharin would probably facilitate metabolic control in the obese, adult-onset diabetic by improving weight loss. In the juvenile-onset diabetic, the replacement of refined sugar by saccharin might provide additional benefit by acutely reducing or limiting blood sugar peaks.

If the consumption of saccharin reduces the intake of refined sugar without a compensatory increase in polysaccharide (starch) ingestion, the size and frequency of hyperglycemic peaks should also be reduced. Insulin-dependent patients and juvenile diabetics of normal weight must compensate for reduced free-sugar intake by increased ingestion of another caloric source in order to maintain body weight. It is both likely and desirable (Weinsier et al., 1974) that most or all of that compensatory increase be derived from polysaccharides rather than fat (Bierman et al., 1974). The potential benefit of saccharin in relation to diminished hyperglycemic peaks would then depend upon whether refined sugar (sucrose) produces larger hyperglycemic peaks than do isocaloric quantities of polysaccharides.

Farkas and Forbes (1965) interviewed 100 adult diabetic women who had used NNS's for at least 1 year to determine the frequency and extent of consumption of NNS's and the relationship of NNS's to the subjects'

adherence to a carbohydrate-restricted diet. They discovered that NNS users (arbitrarily classified as those using NNS's more than once weekly) did not adhere to their diets more frequently than did nonusers. The authors concluded that "there was little basis for implying that adherence or nonadherence to a low carbohydrate diet is related to the use of a noncaloric sweetener." Both cyclamates and saccharin were used by the subjects; however, no quantities of intake were stated. No biochemical measures of diabetic control, e.g., the frequency of hyperglycemic peaks, were taken, nor were data supplied on the type of diabetes that had been diagnosed in the subjects--a key factor in determining the importance of carbohydrates in the diabetic diet (West, 1976).

Stern (1968) reported a 13-month study of 34 diabetics who were users of NNS's and of 14 diabetic controls who were nonusers. The subjects were further divided into obese and nonobese groups. The daily ingestion of saccharin and cyclamate-containing foods was recorded during three periods: a 1-month baseline period, a 6-month period when the use of cyclamates was "encouraged", and a 7-month period when the diet was "supplemented" with capsules containing a 10:1 mixture of cyclamates-saccharin. There were no significant changes in the group averages for body weight, fasting blood sugar, or in the other laboratory indices measured. No weight loss occurred among the obese diabetics even after large doses or prolonged ingestion of NNS's. However, total caloric intake was not measured, and the types of dietary controls that were exercised, if any, were not stated.

In Sweden, Lenner (1976a) studied nine adult diabetics and three controls to test the effect of four isocaloric breakfasts on blood and urinary glucose. The test meal consisted of a basal diet plus applesauce

that had been sweetened with either sucrose, fructose, sorbitol, or a starch/saccharin mixture. The proportions of protein, carbohydrates, fats, and total calories were the same in each case. Contrary to popular belief, there were no significant differences in the effects of sucrose, fructose, or sorbitol meals on blood glucose or on glucosuria. The higher blood glucose levels resulting from the starch/saccharin meal after 60 minutes were significant only in comparison to fructose and sorbitol but not to sucrose. Lenner did not comment on the effect of saccharin per se, but she noted that fructose and sorbitol (a sugar substitute in "diet gum") had no demonstrable advantage over sucrose in maintaining blood glucose levels in well-regulated diabetics.

With the exception of the study by Stern (1968) who noted that blood sugar and body weights were unaffected, there are no published longitudinal data associating saccharin and the control of diabetes (see Table 4-1). So far, there is no evidence to indicate whether or not saccharin or other NNS's are useful in the control of this disease. However, the limited data preclude definitive conclusions.

According to an authoritative review by the Federation of American Societies for Experimental Biology (Talbot, 1978), experts do not support the notion that special dietetic foods are a necessity in the diabetic diet, with the possible exception of water-packed fruits and artifically sweetened drinks. Leading authorities on dietary management affirm that the main emphasis should be placed on controlling caloric intake to maintain ideal body weight, increasing dietary carbohydrates, decreasing fats, and maintaining normoglycemia by avoiding excessive amounts of sucrose and glucose (Talbot, 1978). In another monograph on diet and diabetes, West (1976) states that high carbohydrate diets are well

tolerated by diabetics if total calories are controlled, and that the level of hyperglycemia is related more to the total fuel supply than to the level of dietary carbohydrate. This suggests that sucrose or simple saccharides may have a place in the diabetic diet and that saccharin may be beneficial not so much as a sugar substitute but as an aid to total caloric control.

Juvenile-onset diabetes may present special problems. For adolescent diabetics, diet snacks and beverages contribute to a normal lifestyle and, psychologically, to easier adaptation to peer pressures. Moreover, avoidance of fluctuations in blood glucose levels and hypoglycemia are of prime concern for young insulin-dependent diabetics. However, in well-controlled juvenile diabetics, the type of carbohydrate ingested, i.e., disaccharide versus starch, may not affect the degree of postprandial blood glucose rise; rather, the level of fasting blood sugar may be a primary determinant of the subsequent glucose increment (Lenner, 1976b).

The studies reviewed above do not provide a clinical basis for concluding whether or not saccharin assists in weight reduction or diabetic control.

In the two studies that reported weight loss (Breslow, 1964; Glenn, 1964), it is not clear that all the subjects were overweight or to what degree. However, these reports do not consider individuals who avoided overweight by using NNS's. Nor do the reports examine the efficacy of an NNS as a single component in a multifaceted treatment regimen of a complicated chronic disorder nor do they focus on the extent to which overweight is controlled or motivation for achieving weight loss is attained. The extraordinary constancy of body weight or resistance of weight loss

n a somewhat obese diabetic population has been well documented (Goodner and Oligvie, 1974). However, Davidson (1974) produced significant weight loss (less than 10%) in two-thirds of a patient population at the end of 2 years. He recommended that a weight reduction diet "does not require special or dietetic foods" and discouraged the use of artificially sweetened fruit. Saccharin, other artificial sweeteners, lactose, and sorbitol were allowed "in reasonable amounts."

There has been little attempt to distinguish between obese and non-obese diabetics, or between the juvenile- or adult-onset diabetic--groups for whom the value of NNS's may be inherently different. Studies suggest that whether or not saccharin or NNS's are dietary aids in the prevention or control of disease, they are used extensively by overweight subjects and by diabetics (Alexander, 1962; Farkas and Forbes, 1965; Friedhoff et al., 1971) to add variety to their restricted diets, to satisfy their desire for sweet taste, and, perhaps, to aid with the burden of disease by providing a psychological crutch.

In conclusion, scientific evidence does not indicate whether or not the use of saccharin is directly beneficial to physical health. However, no studies that meet the current criteria for adequate clinical trials have addressed this question explicitly. Five studies concerned with the use of NNS's in managing obesity and the three pertaining to diabetes have methodologic shortcomings.

Both diabetes and obesity are chronic pervasive disorders. To assess the utility of saccharin as an aid in their control, it would be logical to design prospective clinical trials that

- include a sufficiently large, clearly defined representative population,

- closely simulate the normal daily use of saccharin,
- are longitudinal, thereby excluding transient effects,
- are carefully controlled, with a randomized, prospective, double-blind design, wherever possible,
- use quantitative measures of saccharin consumption and of the desired end points, e.g., blood sugar levels and body weights, and
- provide follow-up data.

Such trials have not been conducted. Because of the complex nature of the problems, it might not be practical to design an ideal study.

Commercial and Pharmaceutical Products

Another concern may be the impact of saccharin on the pharmaceutical industry. Saccharin is commonly contained in pediatric drugs, especially antibiotics, vitamins, and aspirin. It is also used in antiasthmatics, anticonvulsants, cardiovascular agents, antacids, sedatives, cold and cough preparations, tranquilizers, and antispasmodics (Adams, 1978). The removal of saccharin from the market may necessitate a reformulation of certain drugs with alternative NNS's. If natural, fermentable sweeteners are substituted, the bioavailability and absorption characteristics of the drugs may be altered. Since saccharin is 200 to 700 times sweeter than sugar, substitution of sucrose may mean enormous pills. Alternatively, if medicines are distasteful, drug compliance by patients may be discouraged (Feldmann, 1977). Also, since natural sweeteners are fermentable and support microbial growth, the shelf-life of drugs, pharmaceuticals, and certain food products may be affected, thereby increasing the economic burden to the consumer. According to a

survey of the 75 members (61 respondents) of the Pharmaceutical Manufacturers Association (Adams, 1978), 619 products marketed by 51 of the 61 firms contain saccharin and products from 10 companies do not. If saccharin were banned, from 6 to 24 months may be required for reformulation where feasible. The estimated cost to 27 companies, which market 414 of the products, would be approximately $170 million. In a testimony to the FDA in June 1977, the Cosmetic, Toiletry, and Fragrance Association (CTFA, 1977) estimated that the initial cost of changing the saccharin content of products to sucrose would be $24 million, and to xylitol, $379 million, as compared to the $1.0 million now spent annually by CTFA member companies to sweeten drugs with saccharin. The cost of replacing saccharin products, the cost of raw materials, and the losses in sales for products that cannot be reformulated would be approximately $200 to 300 million to CTFA member companies.

The efficacy of saccharin alone in masking the bad taste of drugs or increasing their palatability is not uniformly accepted. Schumacher (1968) suggested that a combination of sucrose, sorbitol, and a synthetic sweetener may produce the most palatable product. In a review of the benefits of saccharin, Rosenman (1978) suggested that saccharin-containing drugs be identified. Otherwise no assessment of saccharin as an inert ingredient in drugs can be made.

Consequences of Restriction of Saccharin

Evidence indicates that measurable health benefits cannot be attributed to the use of saccharin. However, Nizel (1977) and Stunkard (1977) suggested that potential benefits may be inferred if the use of saccharin leads to the avoidance of sucrose in conditions such as diabetes, obesity,

and dental caries. Other authorities have voiced concern that removal of saccharin from the market would affect the incidence of obesity (Lee, 1978; Stunkard, 1977). For example, the American Society of Bariatric Physicians estimates that during the 5 years following removal of saccharin, sugar consumption would increase and weight gain would average 6.8 to 10.0 kg per person (Lee, 1978).

The contention that saccharin may be useful in the control or prevention of diabetes and obesity is based on two assumptions: that the removal of saccharin would necessarily lead to increased sucrose ingestion (Stunkard, 1977) and that increased sucrose and nutritive sweetener consumption may increase the prevalence of obesity, leading to a higher incidence of hypertension and hyperlipidemia--both major risk factors in coronary heart disease. In addition, some investigators have suggested that high sugar intake may be directly associated with coronary heart disease.

The assertion that increased sucrose and nutritive sweetener consumption is associated with increased incidence of coronary heart disease is based on the controversial epidemiological data of Yudkin and Morland (1967). Little et al. (1965) found no significant differences in the consumption of sugar among controls and subjects with a history of heart attacks. Walker (1971) contended that coronary heart disease is related to long-term complications of conditions such as diabetes and overweight rather than to a direct consequence of increased sugar intake. Gordon and Kannel (1973) have suggested that there is an acceleration of both coronary heart disease and stroke with increasing degrees of overweight. Whether or not the prevalence of obesity would be influenced by increased sugar consumption would largely depend on the total caloric intake.

A ban on saccharin might lead to an increase in the use of such nutritive sweeteners as sucrose or fructose. At this time, little is known about blood sugar or lipid profiles of diabetic patients who consume mixed meals containing nutritive sweeteners for prolonged periods. Poorly controlled or unstable diabetics could develop hyperglycemia by using nutritive sweeteners liberally. Blood triglyceride concentrations could also be disturbed in a segment of this group. In addition, the liberal use of nutritive sweeteners might possibly influence the formation of glycoprotein and complications of diabetes. But this is still not clear. Daily fructose ingestion of 100 g or more, which can accrue by drinking soft drinks containing this sweetener, could give rise to toxic metabolites. This area needs further investigation, especially in view of the recent increase in the consumption of high-fructose corn syrup (U.S. Department of Agriculture [USDA], 1978). In general, however, there appears to be no scientific basis for the concern that refined sugars (i.e., the disaccharides sucrose and lactose) are "fast" carbohydrates (Bierman et al., 1974) in diabetic subjects. How a ban on saccharin would affect acute blood sugar fluctuations in diabetics is uncertain. However, the nonavailability of NNS's could contribute to other problems in diabetics:

- There may be an increase in ingestion of calories as refined sugar, rather than starch, because of the high caloric density of sugar and its appealing taste,
- There may be less satiety and greater tendency to reactive hypoglycemia following sucrose ingestion than occurs following starch ingestion,
- There may be a greater tendency to hypertriglyceridemia following ingestion of sucrose.

- Meals that are high in refined sugars tend to be low in certain nutrients (e.g., the B vitamins) and in nonnutritive but essential dietary components (e.g., dietary fiber). Therefore, it is possible that the removal of NNS's from the market may ultimately diminish the intake of such important dietary substances through their replacement or dilution with refined sugars.

Figure 4-1 illustrates the trends in sweetener consumption. In general, the consumption of total caloric sweeteners and of the caloric sweeteners plus NNS's has been increasing. Based on USDA (1978) estimates from 1960 to 1969, per capita consumption of NNS's (mainly cyclamate) increased more than threefold, an annual rate exceeding 20%. However, there was no concomitant reduction in total caloric sweeteners or in sugar consumption. Per capita use of total caloric sweeteners rose approximately 1% annually. From 1969, when the ban on cyclamates was announced, to 1971, when the effects of the ban could be fully measured, the per capita consumption of NNS's dropped 7% annually, while use of sugar and total caloric sweeteners continued to increase at about the same rate as before the ban. From 1972 to 1977, NNS's (saccharin only) bounded back to a per capita rate of increase of 8.3% annually. During this period there was a 1% decrease in the annual rate of sugar consumption, which was due largely to the sharp rise in sugar prices from 1974 to 1975. There was no apparent change in the rate of increase of total caloric sweetener consumption. On this basis it would appear that the consumption of NNS's (roughly estimated by USDA, 1978) is not closely associated with sugar or caloric sweetener consumption, and, if measured on a per capita basis, it may not reflect a pattern of substitution for dietary sugar.

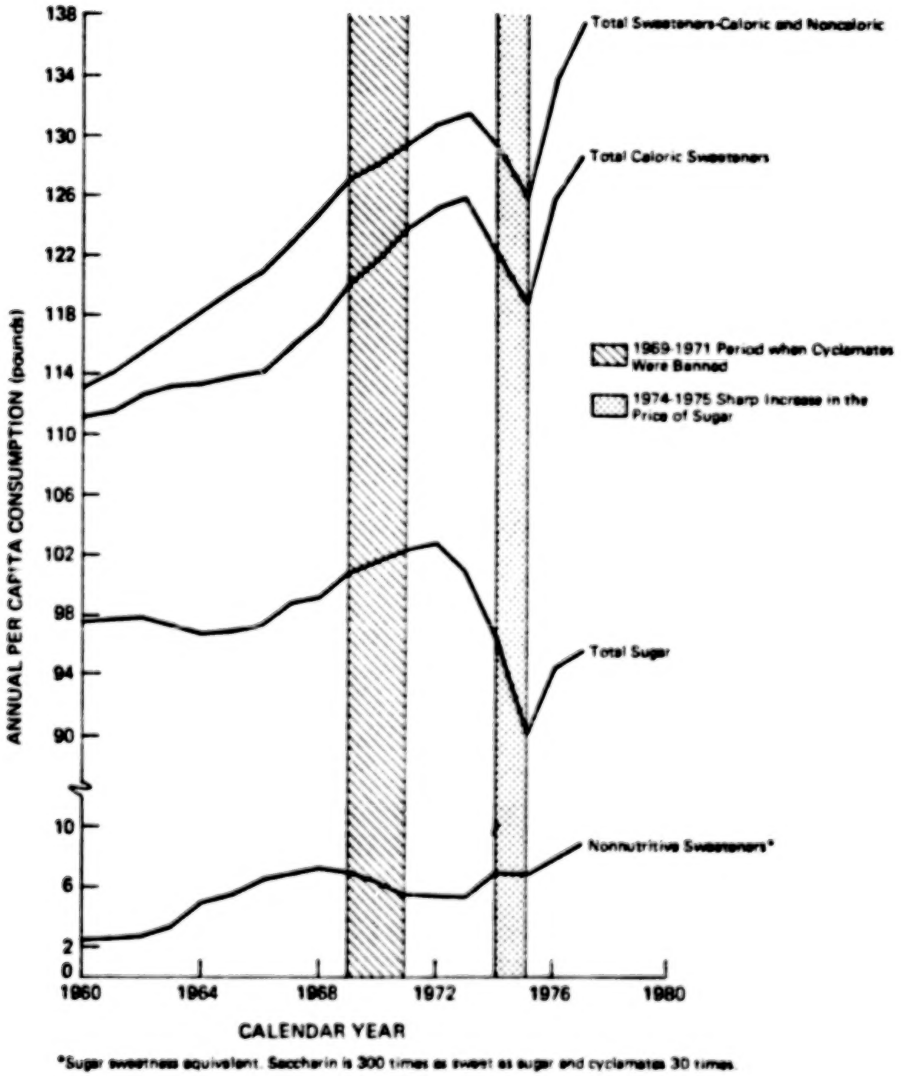

FIGURE 4-1. Trends in per capita sweetener consumption, 1960-1977. Data from USDA, 1968 and 1978.

Two U.S. Department of Agriculture reports give conflicting views on the possible outcome if saccharin is banned. The Agricultural Economic Report No. 364 (March 1977) notes that "Because noncaloric sweeteners are used mainly by people for dieting and so forth, reduced noncaloric consumption would probably not increase caloric consumption by very much" (USDA, 1977b). A May 1977 report by the Economic Research Service (USDA, 1977a) predicts that while over-the-counter sales of saccharin could retain about 10% of the saccharin sales (0.7 billion kg in sugar sweetness equivalent), about half of the saccharin market may be captured by sugar and other caloric sweeteners in the future while about 40% may be completely lost.

In a recent survey of consumer reaction to the proposed ban on saccharin (Parham, 1977), 61% of the participants (from a total of 389) said that they would do without saccharin. Sixty-three percent of the participants would look for other NNS's; but 25% indicated that they would use sugar. This was a small study. Unfortunately, the investigators did not ask what the consumer would do if no alternative NNS's were approved for use. The accuracy of such a survey in predicting consumer actions cannot be judged.

The transitional costs associated with a restriction on saccharin use may also be of consequence. The National Institute for Occupational Safety and Health estimates that about 13 workers are directly involved in the production of saccharin in the United States (Robinson and Ludwig, 1977), and that these few workers produce a major portion of the saccharin that is used in the nation. Thus, the impact of a drastic restriction on the manufacturing industry would be small.

Since most saccharin is consumed in diet drinks, a look at the soft drink industry may give some indication of the transitional costs. This

industry has grown dramatically since 1960 when it held 11.3% of the beverage industry's share (including milk, coffee, juices, etc.). In 1975 its share had grown to 22.0% (National Soft Drink Association [NSDA], 1977). Diet drinks as a percentage of total sales have been increasing steadily since 1963 when they comprised 5.9% of sales of packaged drinks to a high of 11.2% in 1967. Perhaps as a consequence of the ban on cyclamates in 1969, sales of diet drinks accounted for only 7% of the total in 1970 but gradually rose to 12% of packaged sales in 1977 (NSDA, 1978) (see Figure 4-2). This was the equivalent of $1.38 billion in wholesale dollars. By 1985, not only are diet drinks expected to capture a larger share of the total sales but the soft drink industry's shipments of diet and regular drinks are estimated to be worth over $20 billion.

The impact on the packagers, distributors, and commercial users of saccharin would depend on the extent of the restriction and the time over which it would be put into effect. Principally, these would be one-time transitional or reformulation costs. Should the reformulations involve continuing costs, these would necessarily be passed on to the consumer.

The degree to which the dietetic food and beverage industry would be affected by the removal of saccharin would also depend on the availability of adequate substitutes for saccharin.

Some claim that alternative NNS's or dietetic products are ready to be marketed should saccharin be banned. The soft drink industry is said to be considering various alternatives, which include unsweetened products; low-calorie, nutritive sweetener products; or a range of products that permit a choice of caloric intake (Anonymous, 1977). Several NNS's, such as aspartame and neohesperidine dihydrochalcone, are in various stages of development and testing, and petitions for approval have been filed periodically

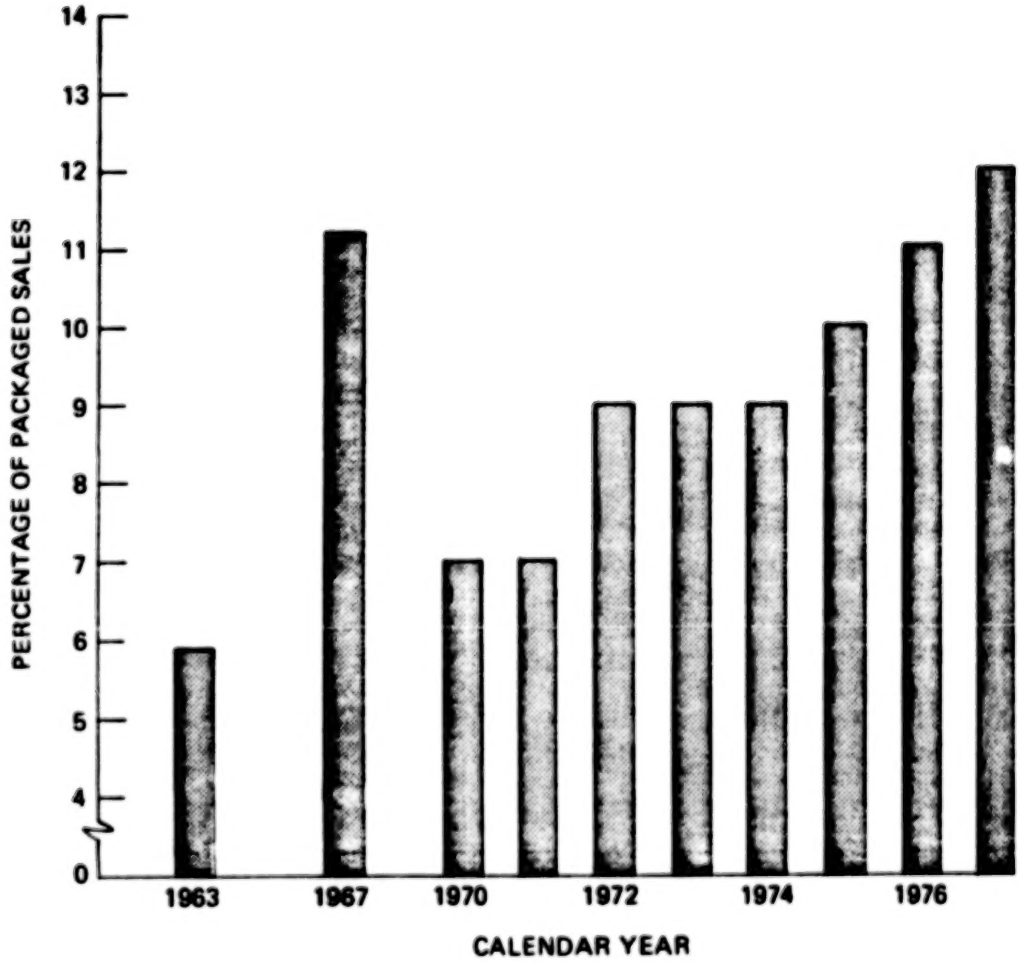

FIGURE 4-2. Patterns in sales of diet drinks as a percentage of the total packaged sales of soft drinks. Data from NSDA, 1978.

with the FDA. However, the possibility of speedily finding an NNS that is safe, economical, and esthetically acceptable for widespread use appears to be remote (U.S. Congress, 1977a). Unfortunately, the committee did not have the opportunity to address this issue.

A more detailed exploration of the economic consequences, favorable or unfavorable, associated with food additive regulations will be discussed in the second part of the report, which will be prepared by Panel II.

PREFERENCE FOR SWEET TASTE

Perhaps no benefits of saccharin have been more strongly asserted and more difficult to quantify than the psychological ones. In an effort to examine the validity of these claims, this section addresses the psychological factors surrounding the desire for sweetness in general and for saccharin in particular. Included are a review of the scientific information relative to taste preference, a description of the population that uses saccharin (thereby demonstrating the perception of a benefit), and a discussion of the manner in which psychological benefits are expressed.

The Desire for Sweets

The desire for sweets as a basic biological drive has been the subject of many studies in animals and of human infant behavior. For example, investigations of taste preference indicate that neonate rats and hamsters demonstrate a strong preference for sweet substances compared to salty, bitter, and sour stimuli (Jacobs et al., 1977). Early psychological research on taste in infants was done by Kussmaul in 1859. He noted that human infants made sucking movements in response to sugar, but grimaces to salt, tartaric acid, and quinine sulfate. Lipsitt (1977) summarized several subsequent studies which indicated that the sweet preference in the human infant may be manifest at birth, before experiential factors

have intervened. DeSnoo (1937) reported increased swallowing in two out of three human fetuses that had been exposed to saccharin, implying that the drive for sweets may even be present *in utero*. However, no solutions aside from saccharin were tested. Although unequivocal statements about the ability of neonates to differentiate taste cannot be made, evidence indicates that infants react positively to sweet substances, but negatively to salt, sour, and bitter tastes.

The cultural and social environment plays an important role in determining the degree of psychological need for sweets. In the American culture, the frequent use of sweets has come to be equated with a sense of enjoyment, celebration, and even a reward for good behavior. However, sucrose is not a necessary ingredient of the diet in all cultures.

Some groups of individuals may desire sweets more than others. While there is some evidence (Engel, 1928) that past experience may influence the liking for sweets, differences in preference may also have a physiologic basis. Grinker (1977) studied obese girls in a summer camp who were on a weight reduction diet. The obese girls found the taste of sucrose solutions to decrease in pleasantness monotonically with increasing sweetness while the girls of normal weight showed no aversion to the sweet taste at higher concentrations. This is in contrast to the observations of Rodin *et al.* as reported by Moskowitz (1977) and to the widely accepted belief that obese children have a strong "sweet tooth." Although the question of taste perception among overweight individuals has not been resolved satisfactorily, it appears to be related to the degree of overweight.

In overweight subjects, taste preference may not be influenced by short-term satiety cues to the same degree as in subjects of normal weight.

The eating behavior of obese animals with hypothalamic lesions is characteristic of impairment in the mechanism of satiety, i.e., food intake does not appear to be controlled by internal mechanisms to the same extent as it is in animals of normal weight (Stunkard, 1975). This concept has been applied in the clinical management of obesity. Schachter (1977) has described the susceptibility of obese persons to environmental rather than internal cues that control food intake. These observations would bring into question the notion of satisfying the sweet taste with limited amounts of foods. One possible inference is that sweeteners, even noncaloric ones, may intensify the desire for sweets in obese individuals instead of curbing it.

Clearly, humans desire sweets. It is equally evident that this desire may increase the incidence of dental caries, overweight, and, possibly, related problems. The convenient availability of a nonnutritive sweetener may abate some of these problems while raising different ones.

The Population Using Nonnutritive Sweeteners

Saccharin is used widely in a variety of foods and by a diversity of individuals. Chapter 2 provides more detailed information on the patterns of saccharin consumption.

The psychological consequences of the unavailability of saccharin may be of particular significance to individuals who use saccharin with greater frequency, especially obese persons and diabetics. The prevalence of overweight varies according to definition and the available population-wide estimates are therefore of limited utility. For example, the first Health and Nutrition Examination Survey (U.S. Department of Health, Education, and Welfare [USDHEW], 1975) estimated that 7.7% to 32% of adult Americans

are obese. If 15% of the population under 20 years of age can be assumed to be obese, approximately 28.7 to 46 million Americans may be obese. Knowles et al. (1976) estimated that diabetics comprise 2% (4.2 million) of the U.S. population. Of these, 5% to 10% (200,000 to 400,000) may be of the juvenile-onset type (West, 1977). If 25% to 38% (Market Research Corporation of America [MRCA], 1978) is assumed to be an accurate reflection of the prevalence of saccharin users, approximately 13.5 to 20.5 million obese and diabetic individuals may be affected should the use of saccharin be restricted. These rough estimates do not include the population at large which, presumably, does not exhibit such a strong need for saccharin. In a 1974 report on saccharin, a committee of the National Academy of Sciences (NAS, 1974) discussed a menu survey conducted in 1967 to 1968. It noted that 60.5% of households with diabetics used NNS's as compared to 19.6% of nondiabetic households. However, since there are many more nondiabetics than diabetics, usage by nondiabetic households accounted for 86% of the total NNS's. While average consumers may be able to satisfy their requirements by substituting other products for sucrose, the removal of saccharin from the market may constitute a form of deprivation for certain segments of the population (e.g., diabetics and overweight persons), which perceive that saccharin is indispensable to them.

Expression of Perceived Benefits

While opinion polls cannot be equated with sound scientific evidence and their validity as accurate predictors of human behavior may be questionnable, their importance as indicators of the preponderance of current public belief cannot be ignored. Therefore, in the absence of scientific

data, the committee has used attitudes expressed by consumers in recent surveys as a measure of the perceived or psychological need for saccharin.

According to a Harris Poll of April 1977, 49% rejected and 36% accepted the statement, "Artificial sweeteners are not an essential part of our diet, and it is not worth risking cancer to have saccharin in our foods" (Harris, 1977a). In June 1977, 43% rejected and 43% accepted the same statement (Harris, 1977b). Forty-one percent of the adult population surveyed (out of approximately 1,500 individuals) used saccharin and 77% of the users indicated that they will continue to use it despite the proposed ban (Harris, 1977b).

In 1977, Parham administered a questionnaire to 389 individuals asking them to summarize their attitude towards the ban. The responses of this small and perhaps unrepresentative sample were compared to a survey performed by the same author with a similar sample in 1969 (Parham, 1970). Selected data from the 1977 survey (Parham, 1978) are shown in Table 4-2. There is an apparent shift in opinion in favor of continued use of saccharin despite the proposal to ban it. In 1969 saccharin was still available as a substitute for cyclamates, whereas currently it is the only legally permitted NNS.

The Calorie Control Council commissioned Market Facts Incorporated (MFI) to conduct two polls. In these polls, approximately 500 health professionals (MFI, 1978b) and 1,480 subjects from the general population (MFI, 1978a) were asked to express their opinions on saccharin.

In the professional opinion poll, physicians estimated that nearly half of their patients "require some form of caloric or sugar intake

TABLE 4-2

Selected Public Responses to a Questionnaire Regarding the Proposed Ban on Saccharin

Questionnaire Statement	Percent Agreement with Statement	
	1977	1969
Have discarded involved product	8.3	33.3
Using up product, will buy no more	5.9	36.8
Will continue to buy and use as long as available	60.6	17.0
Stocking up on involved product	14.2	1.7

Data from Parham, 1978.

control." Generally, the professionals expressed the belief that saccharin was "absolutely essential" or "of great value, but not essential" for the following conditions: diabetes, hyperglycemia, obesity, mild overweight, cardiovascular problems, hypertension, and elevated triglycerides or cholesterol.

The questionnaire focused only on professional opinion regarding the use of saccharin but made no attempt to assess the efficacy of saccharin on a controlled scientific basis in the management of the above-mentioned disorders. About 15% of the physicians and more than one-fourth of the dentists did not name saccharin when asked, "What calorie-free sweeteners are currently on the market?" A third of the dentists were unaware that most toothpaste contains saccharin.

The public opinion survey of 1,480 subjects (MRCA, 1978a) suggested that 25.8% of the population aged 13 and over uses saccharin, and that 91% of all diabetics use saccharin. Responses indicated that saccharin is used to manage overweight, hypertension, high cholesterol, hypoglycemia, and dental caries. These data must be interpreted with caution because the population sample included a larger-than-representative contingent of diabetic and nondiabetic users of saccharin. Furthermore, the questionnaire focused explicitly on the usage and benefits of saccharin and saccharin-containing products while making no attempt to assess comparable usage of regular foods or attitudes towards risk from saccharin.

Obviously, the heaviest users of saccharin are the most concerned about a possible ban. For dieters and diabetics, who represent approximately 25% of the population, artificially sweetened foods provide a more normal and varied diet, thereby contributing to a sense of well-being. The Juvenile Diabetics Association claimed that the impact of a ban on saccharin would be felt particularly by the approximately 300,000 juvenile

diabetics who would be set apart from their social peers if forced to expose their special dietary needs by a ban on saccharin-containing beverages (NAS, 1978).

Numerous letters to the Senate Subcommittee on Health and Scientific Research (U.S. Congress, 1977c), to individual Congressmen, and to the FDA (in one of the greatest volumes received on one issue this decade) are additional testimonials of the intensity of the individual's attachment to saccharin.

Reasoning drawn from the field of economics also reflects the common perception of benefits of saccharin. Particularly in the area of food consumption, some economists believe that a demand for a product reflects consumer benefits unless there are overriding reasons not to do so. In the absence of consumer rejection, the elimination of an economically viable product necessarily involves the loss of valued consumer benefits. A further economic insight rests on the principle that the public will pay more to obtain what it perceives to be a beneficial product. Specific to this discussion is the fact that artificially sweetened chewing gums are occupying an increasing share of the market though they cost 20% more than gum sweetened with sugar.

A restriction on the availability of saccharin would affect different segments of the population differently. The degree of psychological stress that would be imposed by such a restriction would be difficult to quantify. Furthermore, it is difficult to state whether these effects would be transient or whether they would extend over a long period.

The committee acknowledges that there is a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. However, at this time the committee is unable to evaluate this need or to draw conclusions concerning its implications.

SUMMARY AND CONCLUSIONS

The data on the efficacy of saccharin in dietary management of health problems are sparse and, in many cases, inadequate. It is not possible either to rule out totally or to accept the claims of benefits made by some groups. Scientific evidence has not shown whether or not direct benefits to physical health from saccharin exist. However, no study that meets the current criteria for an adequate clinical trial has been conducted explicitly to examine the effectiveness of saccharin in the control of weight or diabetes.

It is not clear that the use of saccharin is associated with a diminution in the incidence of dental caries, for there have been no clinical trials on this subject. There are possible benefits in making dentifrices and therapeutic drugs more palatable in order to promote their proper use.

Human beings appear to have a marked predilection for sweet foods. The committee acknowledges a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. However, at this time the committee is unable to evaluate their significance or draw conclusions about their implications.

Concerning the benefits to physical health:

- Scientific evidence does not permit assessment of the role that saccharin plays in weight control or dietary compliance, both key factors in the prevention or treatment of obesity and diabetes. Five studies on management of obesity with nonnutritive sweeteners and three studies pertaining to diabetes were reviewed by the committee. It considered the design of the studies to be inappropriate for assessing the efficacy of saccharin in weight control or diabetic management.

- The information on the efficacy of saccharin in health maintenance, e.g., the dietary management of health problems is sparse and in many cases inadequate.
- Long-term, well-controlled clinical trials using saccharin to control obesity or diabetes have not been performed. It is uncertain whether a satisfactory study can be designed to answer the necessary questions directly. The committee suggests that attempts at this type of study should continue and that short-term retrospective and other limited studies should be pursued to determine indirect estimates of benefits.
- The long-term consequences to diabetics of increased reliance on nutritive sweeteners have not been examined adequately.
- A recent authoritative review by FASEB does not support the opinion that most dietetic foods are necessary to the diabetic diet. Despite the lack of experimental evidence of efficacy in the dietary management of chronic disease or the maintenance of weight in the normal individual, some attention must be given to the strong preponderance of practitioners' opinion that favors the use of NNS's in weight reduction or treatment of diabetes.
- Although the data are not conclusive, they indicate that saccharin may have potential as a noncariogenic substitute for sugar. It may have a bacteriostatic effect and may lead to reduced plaque formation in the short term, but its noncariogenic effect has not been studied clinically.
- There are possible benefits in making dentifrices and therapeutic drugs more palatable in order to promote their proper use.

- Substitution of sugar for saccharin in snack foods and possibly in soft drinks, should it occur, can be expected to lead to an increased incidence of dental caries.
- There are varying estimates and only limited data to indicate the extent to which sugar would be substituted for saccharin, should saccharin become unavailable. From 1969 to 1970 there was a decrease in the per capita use of nonnutritive sweeteners that reflected the ban on cyclamates. This was not followed by a measurable change in the rate of increase of the use of nutritive sweeteners. In addition, the association of increased sugar consumption with obesity or related health problems is unclear.

Regarding psychological implications:

- Human beings have a strong desire for sweets. Available evidence does not indicate the extent to which this represents a combination of an innate biological need and an acquired preference.
- Public opinion polls suggest a perceived need or psychological reliance on nonnutritive sweeteners by certain segments of the population. Therefore, if saccharin were removed from the market, a significant segment of the population may experience psychological stress of a transient or long-term nature. Some special groups, e.g., juvenile diabetics, may be particularly affected if low-calorie foods and beverages that permit them a more normal lifestyle are removed without suitable replacement. At this time, the committee is unable to evaluate the implications of such psychological reliance on saccharin.

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